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RESULTS OF X-RAY THERAPY IN THYROTOXICOSIS[1]

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Introduction

X-RAY therapy has never received due consideration in this country as a means of treating suitable cases of thyrotoxicosis. The English literature contains but few reports of its use, among which are the papers of Barclay and Fellows (1926), Hayes (1927), Clarke (1928), Don (1934), and Poulton and Watt (1934, 1937). In America X-ray therapy has attracted more attention, and among published papers are those of Means and Holmes (1923), Groover, Christie, Merritt, Coe, and McPeak (1929), Pfahler (1934), Harris and Rose (1936), and Newman and Garland (1938).

To-day the treatment of thyrotoxicosis is almost entirely surgical, with medical treatment reserved for the slighter cases or regarded merely as a pre-operative measure. Other forms of therapy are viewed with suspicion. The lack of enthusiasm for X-ray therapy is largely due to ignorance of its capabilities and limitations, coupled with the relative lack of X-ray therapy apparatus as compared with the number of surgeons who are willing to undertake the operation of thyroidectomy. The ignorance is mainly due to the shortcomings of papers describing its use, for they have usually devoted much more space to descriptions of X-ray technique than to the types of case treated. In many reports details of the clinical states of the cases have been scanty, or the series briefly described as 'unselected' or 'consecutive cases'; follow-up intervals have often been too short, and some results based only upon questionnaires sent through the post, instead of on interview and clinical examination. A clinician contemplating X-ray therapy for a case of thyrotoxicosis is not helped in his decision by a mere statement that of *X* unselected cases of thyrotoxicosis *Y* were cured and *Z* unimproved, for he must know precisely which types of thyrotoxicosis were treated, which responded or were not improved, how long adequate treatment took, and what risks were incurred.

Whatever views are held regarding the distinction between Graves' disease or primary thyrotoxicosis and secondary thyrotoxicosis or toxic nodular goitre, the fact remains that dangerous cardiac complications are commoner in the latter group, yet in many reports no mention is made of the results obtained in secondary thyrotoxicosis. The clinician is therefore left wondering whether such cases, if treated at all, were included among the successes or

[1] Received April 17, 1941.

buried without comment among the failures. It is essential, therefore, that a follow-up study of X-ray treated thyrotoxicosis should embody, apart from details of radiotherapeutic technique, a precise description of the types of case treated and a full discussion of results, obtained after an adequate interval, and based, from clinical examination, upon some simple criteria. In this way only can the value and limitations of X-ray therapy in thyrotoxicosis be truly assessed. The purpose of the present paper is to attempt to fulfil these obligations.

Previous follow-up studies. No useful purpose would be served by a detailed analysis of previous reports on the treatment of thyrotoxicosis by X-rays, as comparisons are virtually impossible owing to the use of different radiotherapeutic techniques, variable follow-up intervals, and diverse criteria of cure or improvement. Table I embodies some published results in approximately comparable form.

TABLE I

Authors	Cases	Cured	Improved	Not improved	Untraced, died, etc.
Means and Holmes (1923) .	58	17	23	18	0
Barclay and Fellows (1926) .	300	190	75	15	20
Hayes (1927) . . .	100	62	14	0	24
Clarke (1928) . . .	44	18	13	7	6
Groover, Christie, Merritt, Coe, and McPeak (1929) .	305	271	26	8	0
,, ,,	26	24	1	1	0
Don (1934) . . .	93	38	30	25	0
Poulton and Watt (1937) .	30	21	9	0	0
	956	641			

The table shows that of all types of thyrotoxicosis treated successful results were obtained in 641 (67 per cent.) of 956 cases, but, as observed above, this information is of little value without details of the types of case treated.

Theoretical Considerations

The thyroid glands of normal laboratory animals are said to be unaffected by X-rays or radium in doses similar to those used to treat thyrotoxicosis in human beings (Walters, Anson, and Ivy, 1931; Eckert, Probstein, and Galinson, 1937). In addition, Pfahler (1934) found no hypothyroidism in cases of laryngeal or pharyngeal carcinoma treated by X-rays in greater total dosage than that used for thyrotoxicosis. Friedman and Blumgart (1937) found that if a thyroidectomy for non-thyrotoxic heart failure had not been total, they could not destroy the thyroid residue by X-rays, and further operation was needed. No histological differences were observed in the irradiated residues as compared with the gland tissue removed previously, although the X-ray dosage used was several times greater than that employed for thyrotoxicosis. There is, however, much evidence that hyperplastic thyroid epithelium, experimentally evoked in animals by various methods, can be reduced or its development checked by X-rays in doses similar to those used for thyrotoxicosis in human beings (Walters, Anson, and Ivy,

1931; Eckert, Probstein, and Galinson, 1937). Furthermore, Zimnitsky (1936) could reduce or stop by post-operative X-irradiation the compensatory epithelial hyperplasia in the residual thyroid tissue of rabbits after partial thyroidectomy. It appears, then, that X-rays in ordinary therapeutic doses will not affect a normal thyroid in man or animals, but that epithelial hyperplasia produced experimentally can be diminished or prevented in animals.

The exact mode of action of X-rays on the hyperplastic thyroid epithelium of thyrotoxicosis is not known, although their beneficial effects in suitable cases are undeniable. The main reason for this is lack of histological material, for the thyroids of successfully treated patients are not subsequently removed, except by chance at autopsy, while portions of the thyroid, in spite of its accessible position, cannot for cosmetic reasons be removed during treatment. Such a lack of material practically precludes, for examination of the human thyroid, the special histological methods employed in the experimental work of Loeb (1919, 1920 *a*, *b*).

Histological examination of a few irradiated thyroid glands, which became available by chance from patients treated for thyrotoxicosis (not in this series) did not, by ordinary staining methods, show any gross or characteristic changes as compared with similar non-irradiated glands. Hill (1938) quoted Barton as holding the same opinion. The examinations did, however, show that there was no obvious diminution in the thyroid epithelium, excessive fibrosis, or interference with blood-supply. This suggested that the X-rays acted directly upon the epithelial cells themselves, and not by any gross changes in their environment. Spear and Glücksmann (1938) showed experimentally that cells were most vulnerable to the action of X-rays in their premitotic phases, but for reasons stated above this cannot be shown in thyrotoxicosis, although mitotic figures are but rarely seen in hyperplastic thyroids removed surgically without any previous irradiation. This is possibly due to the influence of pre-operative administration of iodine.

Whatever the exact mode and site of action of X-rays, it is reasonable to assume that they render the hyperplastic thyroid epithelium innocuous without destroying or obliterating it, thus producing the same end result as surgical removal, but by more subtle means.

X-ray Technique

The X-ray therapy was given to the patients of this series (excepting two) by Dr. Ff. Roberts, to whom I am indebted for the following description of his technique (previously quoted by Martin, 1939):

'The particulars of X-ray treatment are as follows:

'150 kv. filtered through 0·5 mm. Cu. + 1 mm. Al., employing two lateral fields 10 cm. in diameter, at 23 cm. distance. Treatment is normally given fortnightly, each treatment consisting of a dose of 215 r of each of two lateral fields covering the thyroid. If any erythema develops, the intervals between the treatments are lengthened. In the first instance six such applications are given, the first two or three while the patient is in hospital. The rest

of treatment, but it is still salutary to recall that Hale-White (1910) recorded recovery in 70 per cent. of his traced cases of thyrotoxicosis with medical treatment alone. It has been stated that the beneficial effect of X-rays on thyrotoxic patients is due to suggestion, but the early improvement in suitable cases and uncommon examples of relapse after apparent cure do not support this view.

The main difficulty in any follow-up study is to evolve a satisfactory grading of results which will make allowance for individual factors. Gradings are hardly fair or satisfactory when they depend on isolated clinical signs, such as residual lability of the pulse or slight exophthalmos, for these do not represent the whole clinical picture while the thyrotoxicosis is active and cannot take into account the patients' economic or social efficiency after treatment. The assessment of results in this series has been based on the patients' ability to resume the full life or occupation to which they were accustomed before the onset of thyrotoxicosis. The classification used was:

Grade I indicates full ability to resume normal life or work, without any remaining symptoms.
Grade II implies some restriction of work or activity.
Grade III indicates a state of invalidism.

It was found necessary to introduce a sub-group of Grade I—namely, Grade I A—for patients who were perfectly capable of resuming their normal lives, but who had some liability such as hypertension, diabetes, or other condition likely to be permanent or progressive. It is not implied that such liabilities are direct or indirect sequels of thyrotoxicosis, but they do represent potential sources of trouble, and must, as such, be reckoned with.

This classification has the disadvantage that patients in the same grade cannot be compared with each other; for instance, a labourer able to resume hard manual work would be placed in Grade I, together with a clerk able to resume office work, yet the latter might well be incapable of manual labour. Provided this limitation is understood, the classification is practical, and embraces the patients' ultimate efficiency, which is the real criterion of success and so often neglected in gradings based on purely technical factors.

It is fully realized that thyrotoxic patients nearly always retain some of the physical signs present before treatment by surgery or X-rays, but if they regain social and economic efficiency it seems unreasonable to mark down the results of treatment on account of some sign, such as residual exophthalmos, which does not constitute a physical handicap. It is not admitted, moreover, that these residual signs of toxicity can be confidently ascribed to dysfunction of the thyroid gland, although in our present ignorance of the cause of thyrotoxicosis the gland must remain the site of surgical or radio-therapeutic attack.

Results

The results in 42 cases whose interval between the end of X-ray therapy and the follow-up exceeded three years are shown in Table II.

TABLE II

Grade at Follow-up

Type	I	IA	II	III	Dead	Total
Primary, mild	1	2	2	0	0	5
Primary, moderate	8	5	7	0	2	22
Primary, severe	3	0	1	0	0	4
Secondary, mild	0	0	1	0	0	1
Secondary, moderate	0	1	0	0	0	1
Secondary, severe	0	0	0	1	4	5
Total (toxic cases)	12	8	11	1	6	38
Non-toxic goitre	0	0	4	0	0	4
Total (all cases)	12	8	15	1	6	42

This table shows the following main points for further discussion:

(i) Of 31 cases of primary thyrotoxicosis, 19 (61 per cent.) were in Grades I or IA, 10 were restricted in activity, and two were dead.

(ii) Of seven cases of secondary thyrotoxicosis, one was in Grade IA, one in Grade II, one bedridden, and four were dead.

(iii) All four cases of non-toxic goitre were unimproved and restricted in activity.

Primary thyrotoxicosis. Taking the primary cases as a whole, 12 were put in Grade I (1 mild, 8 moderate, and 3 severe).

Of the 7 cases in Grade IA (2 mild and 5 moderate), 6 had hypertension and 3 of these hypothyroidism as well, the remaining case was an alcoholic with a fibroid lung from healed pulmonary tuberculosis.

Of the 10 cases in Grade II (2 mild, 7 moderate, and 1 severe), 3 were still slightly thyrotoxic, although much improved; one of them had relapsed $2\frac{1}{2}$ years after treatment in spite of a transient phase of hypothyroidism lasting a year, and his history is mentioned later in the section on hypothyroidism. One patient had hypothyroidism and severe scarring of the neck with tracheal distortion, and the remaining patient had diabetes and exophthalmic ophthalmoplegia. Two cases had died, one of pneumonia a year after treatment, and the other of rheumatic carditis during the course of which she had developed Graves' disease while in hospital. Review of the reasons causing these patients to be graded down at the follow-up shows that only three were still thyrotoxic, so that it is fair to claim relief of thyrotoxic symptoms in 28 (90 per cent.) of 31 cases, although, for other reasons, only 19 (61 per cent.) could be included in Grade I or IA. Two points of special interest, meriting further comment, may also be noted, namely, the striking association of hypertension and the frequency of neurosis and anxiety states after relief of thyrotoxic symptoms.

Hypertension. Seven of the 31 cases of primary thyrotoxicosis were found to have hypertension at the follow-up examination; five were female and two were male (see Table III).

TABLE III

Sex and age of patient	Blood-pressure in mm. of Hg. at follow-up	Degree of primary thyrotoxicosis
Female, 48	175/100	moderate
Female, 50	215/120	moderate
Female, 50	170/105	moderate
Female, 26	165/90	mild
Male, 50	185/95	moderate
Female, 41	200/105	mild
Male, 23	160/110	moderate

None of these patients had cardiac failure, arrhythmia, valvular disease, albuminuria, or clinical arteriosclerosis, and two of them, aged 23 and 26 years, were well below the age-group at which hypertension might be expected. Parkinson and Hoyle (1934) reported 100 cases of hypertension, of whom 91 were females, associated with active florid or masked thyrotoxicosis, but tachycardia or auricular fibrillation were common also among those who did not have cardiac failure. Hill (1938) noted 20 (10 per cent.) of 205 cases of treated thyrotoxicosis with a diastolic pressure exceeding 95 mm., of whom 50 per cent. were below the age of 40 years. He concluded that the association was more than a coincidence, but found no treatment of any avail. This last point suggests that the cause of the hypertension is not due to hyperthyroidism, while Treadgold (1933) noted a distinctly higher blood-pressure in young men with simple non-toxic goitre than in similar normal men, and Kerpolla (1924) considered that thyroid over-activity played no part in essential hypertension. The exact association of hypertension and treated thyrotoxicosis cannot be determined without a control series of non-thyrotoxic persons of similar age, so that it is only noted in passing.

Anxiety states and neurosis. The striking incidence of incapacity due to these causes in patients relieved of their thyrotoxic symptoms may be explained on the hypothesis that primary thyrotoxicosis is a disease combining thyroid dysfunction with a constitutionally unstable nervous system. These two main constituents of the disease may be present in variable amounts, so that if the nervous instability is prominent, it will not be relieved by surgical removal or irradiation of the thyroid, and the symptoms will still persist after treatment. This is also the probable reason why very mild and doubtful cases of primary thyrotoxicosis respond badly to X-rays or surgery, as removal of the small thyroid element of the disease unmasks the background of nervous instability, but cannot improve it. The hope for better results in these cases lies in better medical and psychological treatment of the nervous instability.

Secondary thyrotoxicosis. Of the seven cases treated none were graded I at follow-up, but one was in Grade I A on account of hypothyroidism.

One case in Grade II had hypertension and clinical arteriosclerosis, and one case in Grade III was bedridden with cardiac failure and auricular

fibrillation. The four patients who died all failed to respond to X-rays, and three of them with cardiac failure and auricular fibrillation were submitted to thyroidectomy as a forlorn hope, with a fatal outcome. These melancholy results naturally militated against further use of X-rays in secondary thyrotoxicosis, and no such case was treated after 1935. It seems clear that secondary thyrotoxicosis, with its grave cardiac complications, is not suitable for X-ray therapy when rapid and brilliant results can be obtained by thyroidectomy. Barker, Bohning, and Wilson (1933) stated of thyrotoxic heart failure that 'there is no other type of chronic heart disease in which so nearly a complete recovery is possible' (with adequate thyroidectomy), while Dunhill (1937) recorded the return of regular rhythm after thyroidectomy in 248 (81 per cent.) of 305 cases of thyrotoxicosis with heart failure and auricular fibrillation. Furthermore, the literature records no undoubted cure of thyrotoxic heart failure or fibrillation by X-rays. Clarke (1928), among 44 cases of thyrotoxicosis treated by X-rays, recorded 25 with auricular fibrillation, but did not specifically state in his results whether the fibrillation ceased or whether the patients were included in his apparent cures. Mild and moderate cases of secondary thyrotoxicosis are prone to progress inexorably to ultimate cardiac failure or auricular fibrillation, and it does not seem justifiable to withhold surgery in favour of X-rays when no reasonable guarantee of protection from these complications can be offered by the latter.

Cases treated by X-rays and surgery. Seven patients of this series were treated both by surgery and X-rays. Three of them (mentioned previously) were examples of severe secondary thyrotoxicosis who failed to respond to X-rays, and were submitted to thyroidectomy as a desperate measure, but with a fatal outcome. The four remaining cases were treated by X-rays, having relapsed after a previous partial thyroidectomy. Their details are as follows:

A. *Non-toxic goitre and anxiety state.* A female school teacher, whose home life was most unhappy, had had ligation of the superior thyroid arteries at the age of 33 years. A year later (1924) she was given X-ray therapy by the late Dr. Shillington Scales. At the ages of 36 and 48 years she had had partial thyroidectomies. Histological examination of thyroid tissue removed at the latter operation showed a cystic, degenerate colloid goitre. Her condition at follow-up was unimproved and she was put in Grade II, and she was an example of the type of case which neither surgery nor X-rays can be expected to improve.

B. *Severe primary thyrotoxicosis.* A man who had had a hemithyroidectomy in 1927, followed by a relapse and X-ray therapy in 1929. He did well and was Grade I at follow-up 7½ years later.

C. *Moderate primary thyrotoxicosis, passing into neurosis.* A man who had had a partial thyroidectomy in 1932 for thyrotoxicosis proved histologically. Only slight improvement followed, and in 1933 his basal metabolic rate was + 24 per cent. He was treated by X-rays, but at follow-up in 1938 he denied any improvement or ability to work; he had no signs of thyrotoxicosis, and was put in Grade II on account of neurosis.

D. *Moderate primary thyrotoxicosis, diabetes mellitus, and exophthalmic ophthalmoplegia.* A woman who had had a hemithyroidectomy in 1927 at the age of 27 years was found to be diabetic in 1928. At the age of 34 years, being still thyrotoxic, she was treated by X-rays. Exophthalmic ophthalmoplegia was diagnosed three years later. At follow-up she was no longer thyrotoxic, but was put in Grade II on account of the associated conditions.

No definite conclusions can be drawn from these cases, but it is fair to say that neither cases B, C, nor D retained any thyrotoxic symptoms or signs, although C and D were partially incapacitated for other reasons.

Case A was clearly unsuitable for either X-rays or surgery.

Non-toxic goitre. Of the four cases treated by X-rays all remained unimproved and restricted in their activities.

They were treated under the impression that they were thyrotoxic cases, but review of their histories and examination at follow-up revealed the diagnostic error. All the patients had goitres with varying degrees of anxiety state and corresponded to the descriptions of 'autonomic imbalance' (Kessel and Hyman, 1923) or to 'Basedow's disease with no thyrotoxicosis' (Rasmussen, 1937). The lack of improvement from X-ray therapy was to be expected, and equally poor results would have followed surgical treatment.

Progress

In patients who were suitable for X-ray therapy, improvement occurred after the first two or three treatments, and continued in a fairly definite sequence as follows:

(i) Decrease in nervousness and sweating.
(ii) Increase in strength and energy.
(iii) Gain in weight and decrease in appetite.
(iv) Drop in pulse-rate, as estimated at the end of each therapeutic session.

The goitre diminished in size rapidly, but exophthalmos, although usually reduced, frequently did not disappear (also a common finding after thyroidectomy). The pulse usually retained its lability on emotion or exertion, but this is considered as a basic constitutional factor rather than a purely thyrotoxic manifestation. Patients often declared that their pulses, which raced when they attended for therapy or examination, were normal when they were at home, and a definite drop in rate was observable at the end of therapy or examination, compared with that on arrival at hospital. Probably the best indications of progress, apart from the patients' own estimates, were a falling pulse-rate and rising weight chart. Basal metabolism estimations were not done, mainly because patients often attended for treatment or follow-up from some distance and therefore needed a good meal before starting. Furthermore, the test gives no more reliable information than careful clinical observation, as has been stressed by Martin (1940), who also quoted Moller (1927) as being unable consistently to correlate alterations in

the basal metabolic rate level with clinical changes in patients undergoing X-ray therapy. The patients' own estimates of improvement have been found particularly reliable, and it was striking that patients who were in reality not thyrotoxic at all insisted that they felt no better after treatment.

It was noticeable that patients continued to improve after cessation of the X-ray therapy, sometimes up to six or nine months after the last treatment. Of the patients who did well the majority felt quite normal again about 12 or 18 months after the first treatment, although many of them had resumed normal life or occupation before that time. No relationship existed between the length of the history of active thyrotoxicosis and the duration of treatment, nor did age appear to have any influence, except that liabilities such as hypertension, which necessitated a grading of I A or lower at follow-up, were naturally commoner in the older patients. In general, the more severe cases needed more treatment than the mild ones, but there were exceptions to this. It is fair to say that treatment, including periods of rest for fear of producing telangiectasis or for observation, occupied an average of six months, and that should be regarded as a minimum period of incapacity for the patient. Every case must remain an individual problem, but in those who respond well a return to normal life and well-being can be expected in about one year.

Cosmetic blemishes. The superficial anatomical position of the thyroid renders it peculiarly suitable for X-ray therapy, but its close proximity to the skin may lead to serious cosmetic blemishes if X-ray dosage is excessive or filtration inadequate. In the earlier years of X-ray therapy scarring and telangiectasis were common, but with improvement in technique these no longer occur, and it is well known that the skin of thyrotoxic patients is more sensitive than that of normal persons. Many surgeons are prejudiced against the use of X-rays on the grounds that scarring of the neck tissues embarrasses any subsequent surgery, but Walton (1923) and Joll (1932) have denied this, and Hill (1938) has quoted Graham to the same effect.

The blemishes which may be found after X-ray therapy for thyrotoxicosis are keloid scarring of the skin with telangiectasis, or telangiectasis alone on otherwise supple skin. The larynx and trachea may also be found to be less mobile than usual in the neck, without any scarring or skin blemish whatever. The radiotherapist is in a difficult position because telangiectases often take at least a year to develop, by which time treatment has usually ceased, and there is no warning of them at the time of treatment.

Of the 20 cases in this series treated during the years 1923 to 1932 inclusive, 16 showed some degree of scarring or telangiectasis of the neck, but between 1933 and 1937 only one of 22 cases showed slight telangiectasis, and four a slight fixity of trachea and larynx, without skin blemish. This abrupt cessation of cosmetic blemishes in patients treated after 1932 may have been due to the inclusion of copper in the filter, or to other improvements which contributed to the evolution of the technique described by Dr. Roberts earlier in this paper. In cases outside this series treated since 1937 no scarring or

telangiectasis has yet been observed, and the risk can now be considered as negligible.

Hypothyroidism. Of the 42 cases treated by X-rays six subsequently developed hypothyroidism. Keloid searring of the neck was present in four of them, and it is probable that hypothyroidism was the direct result of X-ray therapy. One patient with no skin blemish at all developed myxoedema some years after treatment, which suggested that the X-rays were not responsible. The remaining patient had a very striking but transient phase of hypothyroidism which began a year after treatment and lasted for one year, being then succeeded by a relapse of thyrotoxicosis for which he was again treated by X-rays. He was the only patient in this series who relapsed after apparent cure. It seems reasonable to state, from the cases in this series, that hypothyroidism directly attributable to X-ray therapy occurred only in patients with gross searring of the neck, and that with improved technique the risk is very small.

Indications and Contra-indications

There is no approach to unanimity among published reports on the indications for X-ray therapy in thyrotoxicosis. Many series have been frankly 'unselected', while others have specified 'Graves' disease', which may or may not mean primary as opposed to secondary thyrotoxicosis. Thus, Pfahler (1934) treated nodular goitres and Clarke (1928) described them as 'excellent roentgenological medical problems', but Means and Holmes (1928) thought that the indications for surgery were stronger. Groover, Christie, Merritt, Coe, and McPeak (1929) recorded good results with 'surgical failures', but Walton (1923) had seen five cases unrelieved by X-rays after hemithyroidectomy. Pfahler had seen brilliant results in large goitres of the non-toxic type, but Clarke described them as purely surgical conditions. Newman and Garland (1938) advocated X-ray therapy for thyrotoxicosis complicating heart disease. From the results of the present series and observations on other cases not included in it, the following suggestions are put forward for the use of X-ray therapy in thyrotoxicosis, together with some absolute contra-indications.

Suggested indications:

(i) Primary thyrotoxicosis of such a degree that severity does not demand early operation, or its mildness suggest autonomic imbalance rather than true thyrotoxicosis.

(ii) Primary thyrotoxicosis in children or adolescents, in whom one is reluctant to advise operation for fear of upsetting the endocrine balance at a critical age.

(iii) Elderly patients with primary thyrotoxicosis and no cardiac failure or arrhythmia.

(iv) Cases of primary thyrotoxicosis in whom partial thyroidectomy has been inadequate.

(v) Patients with primary thyrotoxicosis who refuse operation or whose extreme dread of it threatens mental breakdown.

Contra-indications:

(i) Cases of secondary thyrotoxicosis or toxic nodular goitre.
(ii) Primary or secondary thyrotoxicosis with cardiac failure or auricular fibrillation, whether paroxysmal or established.
(iii) Any case in which the goitre is causing tracheal compression or deviation, or mediastinal pressure.
(iv) Very severe primary thyrotoxicosis where quick relief by surgery is essential.
(v) Cases of non-toxic goitre, autonomic imbalance, or doubtful cases of thyrotoxicosis.

No attempt has been made to compare the relative claims of X-rays or surgery in a case which would be suitable for either form of treatment. Such a decision must rest upon the facilities available for either, and upon certain non-medical considerations such as the patient's economic ability to afford six or nine months away from work during X-ray therapy, and the existence of convenient and comfortable travelling facilities between the patient's home and the therapy centre. It is again emphasized that, in a suitable case, X-rays or surgery can only do the same thing by different methods, namely, the elimination of hyperplastic thyroid epithelium, which is bodily removed by surgery and rendered innocuous by X-rays. Much harm has been done to the reputation of X-rays by their trial in cases where thyroidectomy has not been thought worth while, and it can be stated definitely that a patient upon whom thyroidectomy would confer no benefit would also derive no benefit from X-ray therapy.

Discussion

Having described the results of X-ray therapy in thyrotoxicosis and having suggested the types of case which are likely to benefit by its use, one is bound to consider whether the treatment is really worth while. Both in theory and practice X-ray therapy has many advantages in the treatment of primary thyrotoxicosis, for the empirical operation of thyroidectomy is avoided, subsequent tetany is unknown, the risk of hypothyroidism and cosmetic blemishes is now very small, the treatments themselves are painless, not frightening, and carry no mortality, and the results in suitable cases do not compare unfavourably with those of surgery. The acknowledged drawback of X-ray therapy is that it takes a long time, and many patients of the hospital class cannot afford to be idle for the necessary period of treatment and observation, especially when surgery offers them quicker relief.

Selection of the case suitable for X-ray therapy is often difficult, for not only has thyrotoxicosis itself to be proved beyond doubt, but the essential decision has to be made whether or not a case is of the primary type, and this is, in some instances, impossible on clinical grounds alone. Furthermore,

we cannot as yet separate clearly the thyrotoxic element of the disease from the constitutional nervous instability which is unaffected by X-rays (or surgery), and may still cause incapacity after relief of the thyrotoxic element. The ability to recognize and assess the relative amounts of these two components in primary thyrotoxicosis would be a major advance in our knowledge of the disease, and would lead to better results of treatment by the more extended use of medical and psychological resources in conjunction with X-rays or surgery. Until we possess this knowledge, both X-rays and surgery are at an equal disadvantage, and there seems to be no good reason for abandoning the former on medical grounds. In present circumstances economic and time factors demand consideration, and if a quicker return to social efficiency is essential, then X-rays cannot be preferred to surgery.

Summary

1. Forty-two cases, comprising primary and secondary thyrotoxicosis and non-toxic goitre, were followed up three years or more after X-ray therapy.

2. Relief of thyrotoxic symptoms had occurred in 28 of 31 cases of primary thyrotoxicosis, but for various reasons only 19 (61 per cent.) of this type had been able to resume a normal life.

3. Only one of seven cases of secondary thyrotoxicosis was relieved of symptoms, four had died, and one was bedridden.

4. The four cases of non-toxic goitre were not improved.

5. Certain suggestions for the use of X-rays in cases of primary thyrotoxicosis are given, together with some absolute contra-indications, which include cases of secondary thyrotoxicosis, thyrotoxic heart failure, and auricular fibrillation.

6. Recognition and better treatment of the element of nervous instability in primary thyrotoxicosis would materially improve the results of X-ray therapy or surgery.

This paper is based upon a thesis accepted for the degree of M.D. of Cambridge University. The work was carried out during the tenure of an Elmore Studentship in Clinical Research at Cambridge University and a Leverhulme Research Scholarship of the Royal College of Physicians. My grateful thanks are due to the honorary medical and surgical staffs of Addenbrooke's Hospital for their generous assistance, to Dr. Ff. Roberts for details of his X-ray technique, and to Professor J. A. Ryle for his help and advice.

APPENDIX OF CASES

Year of treatment	Case	Sex	Age when treated (years)	Type of thyrotoxicosis	Duration before treatment	Follow-up findings		
						Grade	Follow-up interval	Other factors
1923	L.T.	F.	21	Primary, severe	5 months	I	13½ years	—
1924	D.S.	F.	34	Non-toxic, anxiety state	5 years+	II	14 years	Previous ligation of arteries, two subsequent partial thyroidectomies
1928	I.B.	F.	27	Primary, moderate	?	Died of pneumonia one year after treatment		
	E.S.	F.	38	Primary, moderate	2½ years	IA	8 10/12 years	Myxoedema; hypertension, B.-P. = 175/100
	K.N.	F.	40	Primary, moderate	1 year	IA	9 4/12 years	Myxoedema; scarring; hypertension, B.-P. = 215/120
1929	A.J.	M.	39	Primary, severe	3 years	I	7 7/12 years	Previous hemithyroidectomy, 1927
	E.U.	F.	52	Primary, moderate	1 year	II	8 years	Myxoedema; scarring
	H.F.	M.	33	Primary, mild	6 months	I	6 9/12 years	—
	I.S.	F.	21	Primary, moderate	6 months	I	8½ years	—
	L.M.	F.	50	Primary, moderate	9 months	IA	9 years	Myxoedema; hypertension, B.-P. = 160/105
1930	E.T.	F.	29	Primary, mild	4 years	II	6 years	Anxiety state
	R.B.	F.	41	Primary, severe	3 years	I	5 8/12 years	—
	A.T.	F.	19	Primary, mild	4½ years	IA	7 8/12 years	Hypertension, B.-P. 165/90
1931	C.C.	M.	39	Primary, moderate	3 years	I	5 years	—
	R.F.	F.	31	Primary, moderate	9 years+	I	6 years	—
	K.C.	F.	44	Secondary, severe	4 months	III	7 2/12 years	Heart failure and auricular fibrillation
	W.W.	M.	50	Primary, moderate	9 months	IA	7 4/12 years	Alcoholism; fibroid lung
	H.W.	M.	21	Primary, moderate	1 month	I	7 years	—
1932	E.M.	F.	50	Secondary, mild	6 months	II	6 years	Hypertension, B.-P. 190/100
	E.P.	F.	25	Primary, moderate	1 year	I	3 7/12 years	—

Year of treatment	Case	Sex	Age when treated (years)	Type of thyrotoxicosis	Duration before treatment	Follow-up findings		
						Grade	Follow-up interval	Other factors
1933	B.P.	M.	23	Primary, moderate	1 year	II	5 years	Previous subtotal thyroidectomy, 1932; neurosis; hypertension, B.-P. = 160/110
	A.B.	F.	29	Secondary, severe	1 year	*Died after thyroidectomy, 1933; no response to X-rays*		
	E.K.	F.	35	Primary, moderate	6 months	I	$3\frac{7}{12}$ years	—
	A.L.	M.	46	Primary, moderate	1 year	IA	$3\frac{5}{12}$ years	Hypertension, B.-P. = 180/95
	C.C.	F.	36	Primary, mild	1 year	IA	$4\frac{1}{2}$ years	Hypertension, B.-P. = 200/105
1934	E.M.	F.	29	Primary, moderate	4 years	II	$4\frac{1}{2}$ years	Previous hemithyroidectomy, 1931; diabetes; exophthalmic ophthalmoplegia
	A.G.	F.	49	Non-toxic	6 months	II	4 years	Hypertension, B.-P. 225/115
	F.S.	F.	20	Primary, mild	1 year	II	$4\frac{1}{2}$ years	Anxiety state
	A.B.	F.	41	Secondary, moderate	2 years	IA	$6\frac{5}{12}$ years	Myxoedema
	A.S.	F.	44	Secondary, severe	15 years	Died after thyroidectomy, 1935;		diabetes; auricular fibrillation
	E.C.	F.	55	Secondary, severe	?2 years	Died after thyroidectomy, 1934;		heart failure; auricular fibrillation
1935	A.F.	F.	31	Primary, moderate	9 months	II	3 years	Anxiety state
	S.M.	F.	73	Secondary, severe	1 month	Died during treatment, 1936;		heart failure; auricular fibrillation
	M.W.	F.	42	Primary, moderate	6 months	I	3 years	—
	P.W.	M.	37	Primary, moderate	3 months	I	3 years	—
	F.P.	F.	24	Non-toxic	6 months	II	3 years	Neurosis
1936	A.M.	F.	33	Primary, severe	9 months	II	3 years	Still slightly toxic
	L.T.	F.	16	Primary, moderate	9 months	Died during treatment;		rheumatic carditis
1937	A.G.	M.	45	Primary, moderate	18 months	II	3 years	Relapsed two years after treatment; still toxic 1940, and treated again
	I.F.	F.	27	Primary, moderate	5 months	II	$3\frac{3}{12}$ years	Still toxic; hypertension, B.-P. 200/80
	A.D.	F.	21	Primary, moderate	9 months	II	3 years	Neurosis
	F.S.	F.	34	Non-toxic	1 year	II	$3\frac{1}{2}$ years	Anxiety state

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THE EFFECT OF LIVER THERAPY ON ERYTHROPOIESIS AS OBSERVED BY SERIAL STERNAL PUNCTURES IN TWELVE CASES OF PERNICIOUS ANAEMIA[1]

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With Plate 1.

Introduction

It has been generally accepted since the work of Peabody (1927) on tibial bone-marrow biopsies in pernicious anaemia, before and after treatment, that remission following liver therapy is the result of replacement of megaloblastic by normoblastic marrow. The present communication records the changes observed in films prepared from sternal marrow in cases of pernicious anaemia before, and at various short intervals after, the initiation of liver therapy. The investigation was undertaken with the following objects:

(1) The determination of the earliest time after the initial injection of liver extract at which cytological changes in bone-marrow take place.

(2) The investigation of the nature of the mechanism underlying the cellular response.

(3) The elucidation of the controversial question of whether normoblastic and megaloblastic series of cells represent distinct lines of development, or whether, under the influence of liver therapy, the former develop directly from the latter.

It is not our intention to review in detail the various theories of red-cell development or the numerous terminologies that have been advanced. The subject is thoroughly dealt with by Dameshek and Valentine (1937), Jones (1938), Israëls (1939), Scott (1939), Whitby and Britton (1939), and Gilmour (1941), whose publications should be consulted for full discussion and bibliographies. However, without wishing to be drawn deeply into the polemics of the subject, we feel it is desirable to summarize the prevailing views on erythropoiesis.

In health and in anaemias other than those due to deficiency in the anti-pernicious anaemia factor, the cytology of the bone-marrow is dominated, as far as the red-cell series is concerned, by the presence of large numbers of relatively mature nucleated red cells from which the erythrocytes develop. It is generally agreed that these nucleated cells are derived from large parent stem-cells, scanty in number and exhibiting deeply basophilic cytoplasm and

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large pale nuclei containing several nucleoli. The process of maturation is characterized by progressive diminution in size of the successive generations of cells, accompanied by a graduated development of haemoglobin within the cytoplasm, so that, as seen in Romanowsky stained preparations, its blue colour undergoes transformation to grey, green, and finally pink. This transformation is accompanied by corresponding changes in the nucleus, which becomes progressively smaller and denser in appearance owing to condensation of the chromatin, resulting eventually in pyknosis and finally in extrusion or absorption of the nuclear remnant, coincident with the production of the mature erythrocyte. Authors differ in their designation of the more immature cell types, but there is general unanimity in using the term normoblast for the more mature nucleated cells, and in referring to this sequence of red-cell development as *normoblastic erythropoiesis* on account of the predominance of normoblasts among the cells concerned.

In the foetus and in anaemias due to lack of the anti-pernicious anaemia factor, the bone-marrow is characterized by the presence of many large immature cells, and by the tendency of the nuclei of the cells undergoing haemoglobination to exhibit a relatively immature appearance. The haemoglobinized cells with immature nuclei are occasionally found in the peripheral blood of patients in the stage of severe relapse in pernicious anaemia and were referred to by Ehrlich as megaloblasts. This type of erythropoiesis is therefore generally termed *megaloblastic*. Some authors, such as Turnbull (1936) and Whitby and Britton (1939), hold that the process is essentially an arrest in maturation characterized by a shift to the left in ripening of the cytoplasm with a relative retardation in nuclear development. It is thought that in pernicious anaemia this interference with maturation is due to lack of the haemopoietic principle, replacement by liver therapy resulting in the megaloblasts in the bone-marrow developing into normoblasts and the restoration of normal erythropoiesis. On the other hand, many recent authors, such as Jones (1938), Israëls (1939), and Scott (1939), consider that the cells formed in megaloblastic erythropoiesis belong to a line of development quite distinct from that of the normoblasts, and that a cell of the megaloblastic series is incapable of developing into a normoblast. It is considered by these authors that following liver therapy megaloblastic blood formation ceases, the remaining megaloblasts developing rapidly into megalocytes which enter the peripheral circulation, and that concomitantly a multiplication occurs of the normoblasts previously present in small numbers, resulting in the restoration of the normal marrow picture.

The nomenclature employed by protagonists of this second doctrine is varied, but most of the authors follow a general scheme based on the conception of an erythroblastic stem-cell referred to by such designations as 'myeloblast', 'erythrogone', or 'pro-erythroblast', which is deemed capable of forming either normoblasts or megaloblasts; but, as already stated, once differentiation has occurred each type of cell is considered capable of maturing only along its own line of development. Each of these series of cells is usually

subdivided into three or more classes according to the degree of maturation. For the interpretation of the erythropoietic significance of morphological

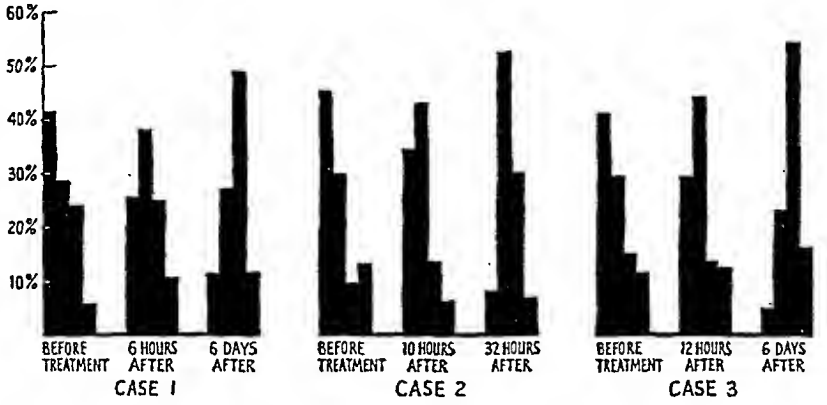

FIG. 1. Pictographs showing relative percentages of the four types of erythroblast present in sternal marrow films from three cases of pernicious anaemia, before and at varying intervals after injection of liver extract. In each group type I, II, III, and IV erythroblasts are represented by the four vertical columns in that order from the left.

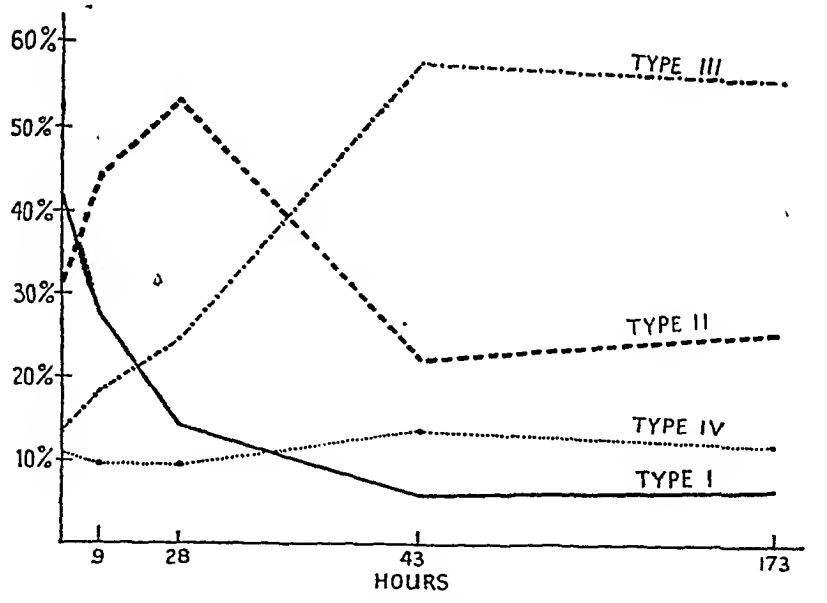

FIG. 2. Graph indicating the relative percentage of types of erythroblast present in sternal marrow films before and after injection of liver extract. The graph was constructed from data obtained by averaging the percentage distribution of cell types in all 12 cases before treatment, and at average time-intervals after commencement of therapy.

changes in the marrow it would therefore be necessary to be able to distinguish with precision between at least seven classes of erythroblast (using this term in its widest sense).

Our own experience with differential counts on marrow films has caused us to regard such a classification as an impracticable working proposition,

for in numerous instances we have found it impossible to decide with any degree of conviction whether a given cell should be classed in the early normoblastic or late megaloblastic series. Dameshek and Valentine (1939) admit this difficulty, stating that: 'It cannot be denied, however, that cells resembling the more mature megaloblasts are occasionally seen in conditions other than pernicious anaemia. It must be admitted that various criteria for diagnosis, even though strictly established, cannot always be used to differentiate with certainty between a mature megaloblast and an immature normoblast.' Again, Scott (1939) states that 'orthochromatic megaloblasts may be indistinguishable from the analogous normoblast of large size'.

We are of opinion that a working classification, as distinct from a hypothetical schema, should be as simple as possible consistent with the separation of clearly defined cell types. We have therefore limited our classification of erythroblastic bone-marrow cells in Romanowsky stained films to the following four types, in which nuclear structure forms the chief point of differentiation. We use the term 'erythroblast' for any nucleated cell deemed capable of differentiation towards an erythrocyte.

Type I. A large cell (average 18 μ diameter) with a variable amount of cytoplasm usually deep blue in colour. No granules are present. The nucleus (average 14 μ diameter) is pale and composed of a fine reticulated scroll-like mass of chromatin. Indistinct nucleoli may be present. This type appears to correspond to the megaloblast of Whitby and Britton (1939) and to include the pro-erythroblast and megaloblasts A and B of Israëls (1939).

Type II. A somewhat smaller cell (average 14·2 μ diameter), the cytoplasm of which is either basophilic or polychromatic. The nucleus is basophilic (average 10·3 μ diameter) and more deeply staining than in type I, and the chromatin is coarser and denser with a tendency to form lumpy masses, but a reticular character is still preserved. No nucleoli are present. This type appears to correspond to the erythroblast of Whitby and Britton (1939) and to include the normoblast A of Israëls (1939). It should be noted that while the majority of cells classified by us in this type are basophilic, a small proportion of the cells with polychromatic cytoplasm and large, coarsely reticulated acidophilic nuclei appear to correspond to the published descriptions of 'polychromatic megaloblasts', e.g. the megaloblast B of Israëls (1939).

Type III. A smaller cell (average 11·1 μ diameter), the cytoplasm of which is usually polychromatic, but may be basophilic or orthochromatic, the nucleus (average 7·3 μ diameter) is very deeply staining, being composed of a condensed lumpy mass of chromatin often exhibiting a 'clock-face' appearance. This cell appears to correspond to the late erythroblast or normoblast of Whitby and Britton (1939) and the normoblast B of Israëls (1939).

Type IV. A small cell (average 9·3 μ diameter) with polychromatic or orthochromatic cytoplasm and a pyknotic nucleus (average 4·8 μ diameter), corresponding to the normoblast of Whitby and Britton (1939).

The erythroblast characteristic of the bone-marrow in pernicious anaemia

Table showing Percentage of Different Types of Erythroblast in Sternal Marrow Films from Cases of Pernicious Anaemia before and after Liver Treatment, and Percentage of each Type of Cell in Mitosis

Case	Time of puncture in relation to commencement of therapy	Percentage of each type of all erythroblasts counted				Percentage of each cell type in mitosis				Peripheral red-cell count, in millions per c.mm.	Percentage of reticulocytes in peripheral blood
		I	II	III	IV	I	II	III	IV		
1	Before	42·0	28·3	24·0	5·7	3·9	3·8	1·3	—	1·3	<1
	After 6 hours	25·7	38·5	25·5	10·3	5·3	4·1	3·0	—		
	After 6 days	11·3	27·7	49·7	11·3	3·3	3·7	2·1	—	1·8	30 = peak
2	Before	46·2	30·4	9·8	13·6	4·1	3·4	2·7	—	2·2	<1
	After 10 hours	35·8	44·2	13·8	6·2	6·2	9·3	2·9	—		(peak = 18 on 5th
	After 32 hours	8·4	53·6	30·8	7·2	—	5·8	8·5	—		day)
3	Before	42·5	29·5	15·7	12·3	2·3	3·7	3·8	—	1·3	<1
	After 12 hours	28·8	45·0	13·6	12·6	4·7	4·3	5·1	—		
	After 6 days	4·7	23·6	55·3	16·4	—	5·4	3·2	—	1·7	21 = peak
4	Before	40·2	38·4	15·0	6·4	3·9	6·2	4·3	—	1·8	<1
	After 8 hours	19·8	51·7	19·7	8·8	5·3	4·5	1·7	—		(peak = 12 on 5th day)
5	Before	38·5	34·0	17·8	9·7	1·3	4·4	2·8	—	1·2	<1
	After 24 hours	19·8	50·7	18·0	11·5	2·5	3·1	1·4	—		(peak = 31 on 5th day)
6	Before	50·8	27·7	13·9	7·6	8·3	4·6	5·7	—	1·2	<1
	After 3 days	7·5	19·7	61·7	11·1	—	5·3	7·2	—		23 (peak = 30 on following day)
7	Before	34·2	30·0	18·3	17·5	5·9	3·3	4·8	—	1·8	<1
	After 3 days	4·8	24·3	46·2	24·7	—	4·2	2·9	—		26 (peak = 32 on following day)
8	Before	44·7	29·3	12·7	13·3	3·6	3·5	5·0	—	1·3	2·8
	After 3 days	9·3	31·7	52·4	6·6	—	2·8	6·5	—		2·2 (peak = 11·4 on 6th day)
9	Before	37·0	38·4	17·1	7·5	7·4	2·9	2·7	—	2·1	1·8
	After 4 days	2·7	11·1	69·8	16·4	—	6·3	4·3	—		13·9 (peak = 27 on 6th day)
10	Before	40·8	32·2	15·7	11·3	3·9	5·6	1·5	—	2·6	<1
	After 5 days	5·4	24·0	59·8	10·8	—	4·8	1·9	—		11·3 = peak
11	Before	38·3	24·0	26·0	11·7	5·3	6·9	10·3	—	1·9	<1
	After 6 days	11·5	21·5	56·5	10·5	1·3	7·5	2·2	—	2·0	35 = peak
	After 10 days	2·3	23·5	58·8	15·4	—	8·6	2·4	—	2·7	19
12	Before	40·2	33·3	15·9	10·6	2·5	3·4	8·1	—	0·8	<1
	After 8 days	4·3	32·5	58·5	4·7	—	3·0	2·5	—	2·0	12 (peak = 30 on 4th day)

during a relapse belongs to type I, while in health and in nutritional and post-haemorrhagic anaemias types III and IV preponderate. In severe cases of macrocytic haemolytic anaemia unresponsive to liver therapy, type II cells may be present in large numbers.

We wish to emphasize that we have adopted this classification solely as a convenience in the performance of differential counts on bone-marrow films with a view to obtaining a picture as clear-cut as possible of the prevailing types of erythroblasts present, and that we have no intention of attempting to add to an already overburdened nomenclature. It should be appreciated that the types I, II, and III tend to merge into one another, and that a certain arbitrary judgement is sometimes necessary for the classification of a given cell which falls on the border-line between groups. Nevertheless, counts checked by an observer who was ignorant of the origin of the films showed good correlation with those done by the first observer.

Methods

Only cases of typical pernicious anaemia in relapse are included in the present series, and the usual haematological data present at the time of sternal puncture are recorded. Each case was punctured before therapy was commenced, and puncture was repeated on one or two occasions after the first injection of liver extract, at intervals ranging from six hours to ten days. The liver extract was either 'anahaemin' or 'reticulogen' given intramuscularly in a single dose of 4 c.c. and 2 c.c. respectively. Sternal puncture was performed by introducing a Salah type needle through the anaesthetized skin and periosteum into the marrow spaces of the sternum at about the level of the third rib. Approximately 0·5 c.c. of marrow juice was aspirated and from it films were promptly made, which after drying in air were stained with Leishman and also in some instances with Giemsa stain.

Differential counts of all nucleated cells were made, 400 to 500 cells usually being counted. In addition, counts were made in which only nucleated cells belonging to the erythroblastic series were included, at least 400 of such cells being counted, each cell being assigned to one of the four types already described, the colour of the cytoplasm, whether basophil, polychrome, or orthochrome, also being recorded. It is on the results of these latter counts of nucleated red cells that our present submissions are based. At the time of each count a note was made of the number of cells of each type exhibiting evidence of mitosis. The determination of the type of cells undergoing mitosis had of necessity to be based on such considerations as size of the cell and character of the cytoplasm, and accordingly lacked precision, since the character of the nuclear structure could not be observed.

Results

The results of the differential counts of the bone-marrow films are shown in the accompanying table, from which it is apparent that within 6 to 10 hours of the initial injection of liver extract a remarkable change in the

cytology of the nucleated red cells occurs. This change consists of a reduction in the mean size of the predominant cell type accompanied by a striking change in the character of the nucleus, which becomes deeper in staining, the chromatin strands tending to present an irregular lumpy appearance. In other words, the cell type II increases in frequency at the expense of type I. The predominant cell of this type has a basophilic cytoplasm, the principal feature distinguishing it from type I being the nuclear change. Reference to the Table shows that this change is not accompanied by any increase in the percentage of mitotic figures commensurate with the remarkable transformation in the appearance of the bone-marrow picture. No definite evidence of amitotic division was seen.

After 32 to 72 hours the change is still more pronounced, for by then the type I cells have become relatively infrequent and the picture is dominated by the type III cells, considerably smaller in size, mostly with a polychromatic cytoplasm and a small, relatively dense nucleus. In conventional terminology, the megaloblastic picture has now become normoblastic. Again no significant increase in mitotic figures is seen.

The changes just described are further illustrated by the pictographs of three representative cases, and by the graph which is based upon the whole series of cases, the percentage distributions of the various cell types being averages calculated for average time-intervals.

Discussion

With regard to the mechanism underlying the widespread cellular change which occurs so rapidly after the injection of liver extract, two possibilities require consideration. Is the change a result of mitotic division of the more primitive cells, or is it a transformation of type I into type II cells without any intermediate cell division, consequent upon some direct physicochemical effect of the anti-pernicious anaemia factor?

The relatively low incidence of mitotic figures and the widespread nature and rapidity of the cellular changes seem to support the theory that the maturation is a direct physicochemical process due to the action of the liver extract rather than the result of cellular mitosis. It must be admitted that we are unaware of any proof of the existence of such a process, although maturation of myeloblasts into myelocytes without cell division has been suggested by Smith (1932). It is possible, of course, that the relatively low frequency of cells seen in mitotis is due to the rapidity of the process, so that only a small number may be recognizable at any given moment. In support of this contention is the finding of only a small percentage of cells in division in the bone-marrow five to six days after the commencement of liver therapy when the presence of many reticulocytes in the peripheral blood indicates marked activity of the bone-marrow. Segerdahl (1935) reported that in sternal marrow films from a case of pernicious anaemia twenty-four hours after injection of liver extract few mitotic figures were

seen, although a striking normoblastic proliferation was present. She concluded that the rapid cellular proliferation must be largely the result of amitotic division, but as has already been noted we encountered no instances of division on the part of the cells concerned which we could positively identify as amitotic.

Concerning the question of whether under the influence of liver therapy megaloblasts develop directly into normoblasts or whether these cells form two distinct lines of development, it appears to us that the rapidity of the change in the bone-marrow from a megaloblastic to a normoblastic picture as described above supports the view that normoblasts can be derived directly from megaloblasts. Furthermore, if the effect of liver extract was to stimulate proliferation of the normoblasts already present in the bone-marrow, the differential counts shortly after injection of liver extract should show a rapid increase of cells belonging to types III and IV, but this has not been found to be the case, the first effect noted being a replacement of primitive megaloblasts by the type II cells.

Finally, differential counts of erythroblasts made by us on sternal marrow films from severe untreated cases of nutritional iron deficiency anaemia, and haemolytic anaemia give figures for the percentages of different cell types comparable with those obtained in cases of pernicious anaemia three days after institution of liver therapy. It would appear, therefore, that under conditions of prolonged and severe strain a reversion of the normoblastic towards the megaloblastic blood picture may occur. If this be correct, it is additional evidence in support of the thesis that megaloblasts and normoblasts belong to one developmental series.

Summary

(1) Sternal marrow punctures have been performed in 12 cases of pernicious anaemia before and at varying periods from six hours to ten days after the commencement of liver therapy.

(2) As early as six hours after the first injection of liver extract, cytological changes are observed in films of sternal marrow-juice. These consist of a decrease in the proportion of primitive megaloblasts and a corresponding increase in number of more mature cells. Three to four days later the predominant erythroblastic cell is a normoblast.

(3) The significance of these findings is discussed.

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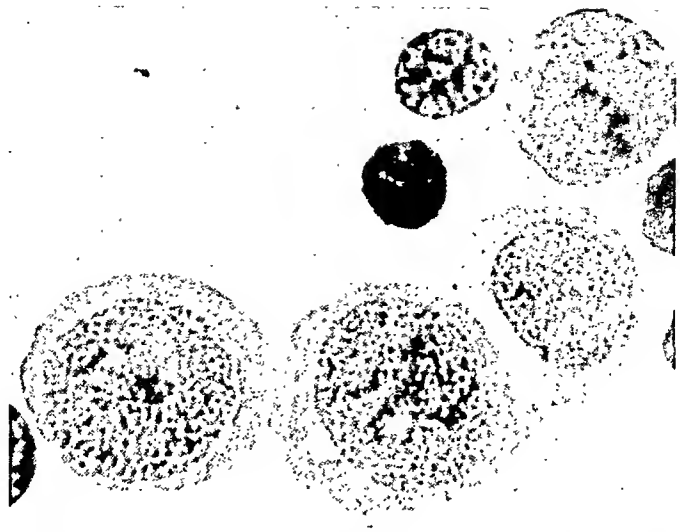

FIG. 3. Photomicrograph showing four type I erythroblasts, ×1600

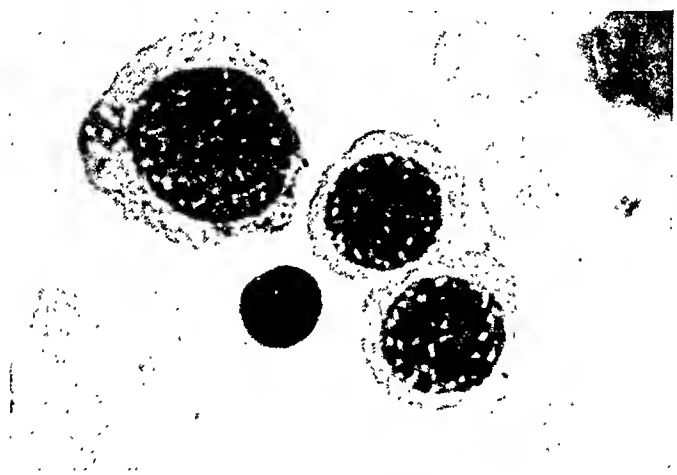

FIG 4. Photomicrograph showing three type II erythroblasts, ×1600

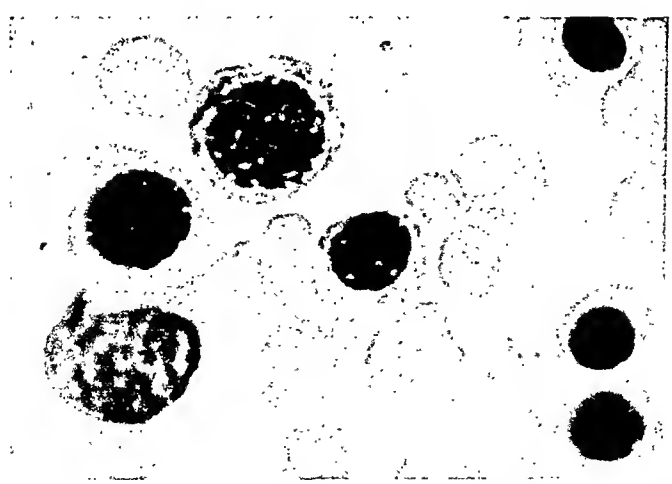

FIG. 5. Photomicrograph showing one type II, three type III, and two type IV erythroblasts, ×1600

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METHYL CHLORIDE POISONING[1]

By A. MORGAN JONES

(From the Manchester Royal Infirmary)

Introduction

Methyl chloride poisoning occurs most commonly from the use of this substance as a refrigerating agent. Few cases have hitherto been reported in this country, and all have been comparatively mild. Porteous (1930), Bridge (1931), and Birch (1935) each described single cases, Sharp (1930) has reported two cases, and Gorham (1934) described one moderately severe case and noted minor ill-effects in four other workmen. Many more cases have been reported from America, and it is to Kegel, McNally, and Pope (1929) of Chicago that we owe the fullest clinical description. Their paper is based on 29 cases, with 10 deaths, which occurred in Chicago in 1928–9. Baker (1927) described 21 milder cases amongst the employees of an American firm of refrigerator manufacturers, and later (1930) a further 75 non-fatal cases.

The seven cases reported in this paper occurred amongst a small number of travelling refrigerator repairers working for a single firm. Six of the cases were of moderate severity, and the seventh is, so far as we know, the first severe case to be reported in this country. In all cases exposure to methyl chloride occurred in the same way. A refrigeration plant (see Figure) consists of a low-pressure side, the evaporator (A), and a high-pressure side, the compressor (B). At room temperature and atmospheric pressure methyl chloride is a gas. In the compressor it is condensed to a liquid. It is then allowed to evaporate into the low-pressure side and so takes up heat, thus cooling the chamber in which the evaporator is placed. From the evaporator it passes back to the compressor by the outlet pipe (C). The usual fault which refrigerator engineers are called upon to repair is a blockage in the evaporator. When this occurs the pressure in the evaporator behind the obstruction becomes equal to that of the high-pressure side, and the methyl chloride condenses in this part of the evaporator. To clear the blockage, the outlet pipe (C) from the evaporator to the compressor is disconnected and the evaporator heated so that the liquid methyl chloride evaporates and expands. The pressure so produced will ultimately 'blow' the obstruction. When this happens the greater part of the methyl chloride charge is forced from the outlet pipe into the room and immediately evaporates. At this stage the engineer should leave the room and wait until the air is clear of

[1] Received April 26, 1941.

methyl chloride. Since the gas is non-irritating and almost odourless, he is apt to believe it to be harmless, so he usually completes his work at once, for to do so he has only to reconnect the outlet pipe and replace the lost charge of methyl chloride. Thus refrigerator repairers are frequently exposed to this gas, for they are unaware or heedless of its dangers.

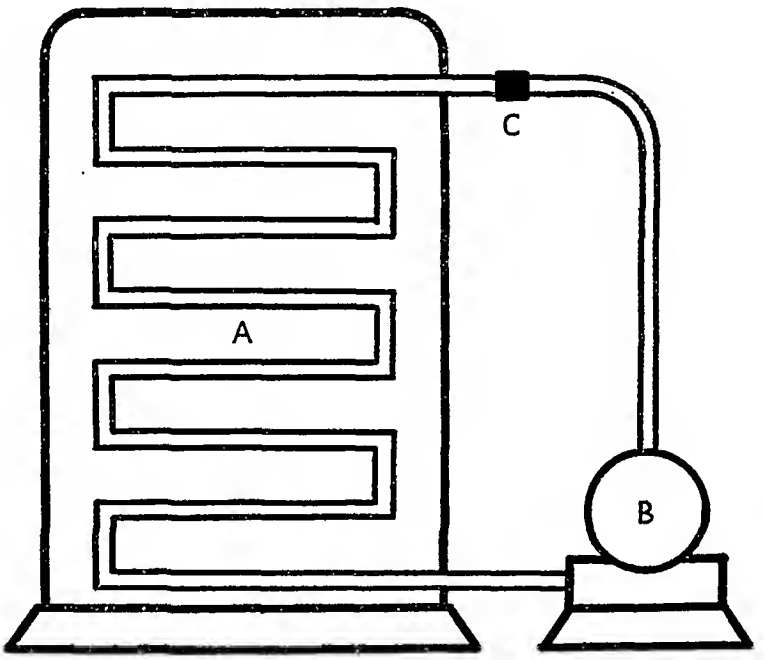
Case Reports

Case 1. R. V., a refrigerator engineer, aged 38 years, was admitted to the Manchester Royal Infirmary, under the care of Dr. A. H. Holmes, on 21 May 1940. He complained chiefly of twitching of the arms and legs after exposure to methyl chloride.

Previous attacks. He had worked with methyl chloride for six years, but it was not until three years prior to admission that he had first suffered severe ill effects. Then, after a leakage of methyl chloride while he was clearing a blocked evaporator, he vomited several times and staggered when he walked. He was very ill for three days, with continual nausea and vomiting, and was unfit to return to work for a month. For some time subsequently he was easily tired and felt unwell. Several months later he had an attack of diplopia lasting two or three weeks. A year later he came home one evening in a confused and drowsy state, complaining that he had inhaled a good deal of methyl chloride owing to a 'blow-out'. He did not vomit, but fell into a heavy sleep. The next morning he left for a week's holiday. During the journey he was drowsy and confused and did not seem to know where he was. He could not walk without aid and complained of misty vision and diplopia. He subsequently remembered nothing of the journey. At the end of the week he was still ataxic both in the arms and legs, but returned to work. His symptoms gradually cleared during the following few weeks.

Present attack. On 17 May 1940 he was engaged in clearing the blocked evaporator of a refrigerator which was housed in an almost unventilated cellar. The whole charge of methyl chloride escaped when the obstruction was cleared. When seen soon afterwards by his supervisor he said that he felt sick and ill, he seemed dazed, his speech was thick and slurred, and he staggered like a drunken man. He had difficulty in driving his car owing to blurring of vision and diplopia, the latter being sufficiently severe to make him cover one eye. When he reached home he could not eat, he vomited, and complained of headache and noises in his ears. He spent a restless night, but insisted on returning to work the next morning, although he felt ill. He remembers nothing of that day, but he is known to have worked all day, although he should have finished at noon. During the morning he replaced a damaged part of the apparatus, but during the afternoon he took the refrigerator to pieces again and undid all his previous work. He was still there at 9 p.m. when he was found apparently drunk, for he staggered about and spoke in a confused way with thick slurred speech. The owner of the refrigerator put him in a taxi and sent him home. At 10.30 p.m. his wife returned home and found him lying semiconscious on the floor just inside the front door. He was roused with difficulty, but did not recognize his wife or relatives. He was given a sedative and slept heavily all night. The next morning he was drowsy and confused, but recognized his wife, although he was unable to say what date it was or where he was. He had no recollection of the previous day. He would eat nothing during the day and was very restless that night. On the following day, 20 May, he was

restless and confused. In the evening tremor of the right arm developed and was so severe that it was impossible for him to drink unaided. That night he slept heavily with a sedative. On the following morning at 6 a.m. his arms started to twitch, especially the right, and at 9.30 a.m. he had a severe attack of twitching of the whole body, which lasted for about two minutes and left him exhausted, pale, and sweating. This was repeated at 10.30 a.m. when his temperature was found to be raised. At 2.15 p.m. he



Refrigerating plant. A = evaporator, B = compressor, C = outlet pipe

had an even more severe attack and that afternoon was transferred to the Manchester Royal Infirmary.

On admission the muscles of the whole of the right arm and left forearm were twitching with sharp, shock-like, localized contractions at a rate of two to four per second. He lay with his knees flexed, and similar twitching of his legs occurred when he attempted to extend his knees. Within a few minutes the twitching changed to strong generalized clonic spasms, followed by generalized tonic spasm with powerful opisthotonus, and spasm of the facial muscles resembling risus sardonicus. Respiration ceased for about 15 sec. and he became cyanosed. Violent generalized clonic contractions of all muscles followed and later settled down into localized shock-like contractions.

Examination showed bilateral ptosis and small pupils which reacted only sluggishly to light. There was some limitation of movement of the eyes to both sides, and spontaneous, irregular, jerking movements occurred, especially on lateral fixation. The fundi were normal. Slurring dysarthria was pronounced. Muscular tone was increased and spontaneous twitching was seen in the muscles of the trunk and limbs, most severe in the arms, especially the right, and was partially controlled by clasping the hands together. There was severe action tremor on using the arms. The tendon reflexes were sluggish but equal, and the plantar responses flexor. No gross sensory loss

was detected. Slight generalized abdominal tenderness was present. The temperature was 101° F., the pulse-rate 100 and the rhythm regular, and the blood-pressure 140/100. The heart and lungs were normal. The condition was diagnosed as toxic encephalitis due to methyl chloride poisoning.

Treatment. The convulsions were controlled with sedatives, and potassium citrate was given in doses of 20 gr. every four hours to alleviate the acidosis which is said to occur. As methyl chloride is a chlorinated hydrocarbon, glucose was also given in large amounts to minimize possible liver damage.

Progress. He had two milder convulsive attacks that evening. The next morning he was confused, did not know where he was, and gave irrelevant and incoherent answers to questions. He was sweating profusely and the sweat had a particularly unpleasant odour. The blood-pressure had fallen to 105/75, but rose in the evening to 130/85, when he became extremely confused and almost uncontrollably restless. His mental condition varied from hour to hour; at intervals he was quite rational. Two days later he had another period of great excitement and confusion, during which he was deluded, had hallucinations, and suffered from increased muscular tremors and profuse sweating. Thereafter he improved slowly, but had occasional severe relapses into toxic delirium, when he became incoherent, confused, and deluded, with hallucinations. On 27 May he had been rational for 48 hours and his twitching had stopped, but gross ataxia was still present. On that night, 10 days after exposure to the gas, he again relapsed into extremely severe toxic delirium which lasted about 12 hours. Further slight relapses occurred, but by 6 June all twitching had disappeared, although he still suffered from severe ataxia of the arms. On 8 July he was discharged from hospital free from symptoms, apart from slight unsteadiness of gait, considerable ataxia of the arms, especially the right, and ineo-ordination of eye movements with a vertical 'nystagmoid' jerking and occasional diplopia on looking laterally. These symptoms improved slightly during the next three months, but subsequently remained stationary, in spite of physiotherapy and re-education, until he was last seen, in April 1941. The diplopia was then sufficiently severe to make him close one eye when shaving. He was quite incapable of carrying on his trade as an engineer owing to ineo-ordination of hand movements which became worse after using the hands for a time.

Investigations.

Cerebrospinal fluid. Full chemical and cytological investigations on admission and two days later showed no abnormality. The resting pressure was 30 to 40 mm. of C.S.F., and the Queckenstedt test was normal.

Sedimentation rate. On admission this was 26 mm. in the first hour and fell to 5 mm. by 18 June.

Renal function. On admission there was a little albumin in the urine, and microscopy revealed red cells but no pus. Albumin was present for five days, but on the sixth day the urine was chemically normal and no red cells were seen. The blood urea was 58 mg. per 100 c.c. on admission. On the fourth day it had fallen to 38 mg. per 100 c.c., and the standard urea clearance was 131 per cent. of the average normal. The urinary output averaged only 26 oz. per diem during the first week, when he was sweating freely. The urine contained exceptionally large quantities of carbonates, which diminished gradually over several weeks.

Liver function. On admission the serum did not give a direct van den Bergh reaction, and contained 0·6 units of bilirubin. On discharge it

contained 0·2 units of bilirubin. Laevulose tolerance tests were performed periodically; the results are recorded in Table I. Ten days after exposure a Takata-Ara test was negative, and quantitative estimation of urinary urobilinogen showed that no significant amount was present.

TABLE I

Laevulose Tolerance Tests (Case 1)

After fasting, the patient was given 50 gm. of laevulose by mouth

Date	Blood-sugar					First hour rise	Second hour rise	Combined rise
	Fasting mg. %	½ hr. mg. %	1 hr. mg. %	1½ hr. mg. %	2 hr. mg. %	mg. %	mg. %	mg. %
22:5:40	86	109	118	114	114	32	28	60
1:6:40	91	105	109	100	95	18	4	22
18:6:40	81	91	91	95	81	10	0	10
22:8:40	86	114	118	102	91	32	5	37
6:9:40	91	—	114	—	95	23	4	27
3:1:41	91	100	109	105	95	18	4	22
25:3:41	86	105	114	109	91	28	5	33

Blood and bone-marrow. On admission a blood count gave the following figures: red cells 4,670,000 per c.mm., haemoglobin 90 per cent., reticulocytes 0·8 per cent., platelets 254,000 per c.mm., and white cells 7,200 per c.mm. (64 per cent. polymorphs).

Dr. M. C. G. Israëls reported on a sternal marrow puncture as follows: 'Both the granulocytes and the erythroblasts show rather low figures, but since the blood count is within normal limits, this probably does not signify any degree of hypoplasia.' The red cells rose slowly to 5,090,000 per c.mm. and the haemoglobin to 100 per cent. by the 28th day. The red-cell fragility was normal.

Blood chemistry. The serum calcium was 10·1 mg. per 100 c.c. and the serum phosphorus 3·8 mg. per 100 c.c. on 22 May. The blood contained no carbon monoxide, and the carbon dioxide combining power was 53 vol. per cent. on 22 May. The blood Wassermann reaction was negative.

Urinary porphyrins. At the suggestion of Dr. R. E. Lane the excretion of porphyrins in the urine and faeces was estimated by Drs. J. N. M. Chalmers, A. E. Gillam, and J. E. Kench, who have published details of their interesting results (Chalmers, Gillam, and Kench, 1940). On admission the daily output of urinary coproporphyrin III was about six times the normal; during the following week it rose still higher to approximately 30 times the normal. The output fell slowly to within the normal range shortly before discharge.

Other refrigerator repairers employed by the same firm were questioned and it was found that almost all had suffered at least minor ill effects. The following case histories are selected from those obtained. In none of these cases was there an opportunity for observation during an attack.

Case 2. R. L., a foreman engineer, aged 40 years. This man had worked with methyl chloride for about 10 years, and had had severe symptoms twice and minor illnesses six or seven times. In January 1940 he was repairing a refrigerator in a cellar when a considerable leakage of methyl chloride occurred. The gas smelt sweet and rather fishy, but he attributed the odour partly to the oil with which methyl chloride is mixed in refrigerators. A few minutes after he noticed the smell he felt 'light-headed', as

though about to lose consciousness under an anaesthetic, and became aware of the 'pumping' of his heart and a buzzing sensation in his head. His limbs seemed heavy and useless, and he staggered about so that he had difficulty in making his way out of the cellar. He soon developed a severe frontal headache 'like a tight band'. The staggering persisted for two or three hours. That night he slept heavily. When he awoke in the morning he was violently sick several times and was troubled by flatulence. For three days the vomiting was severe in the morning and became less troublesome later in the day. He could eat little for several days. He did light work for a week, and for two or three weeks did not feel as well as usual. In his milder attacks the inco-ordination and staggering were slight and of short duration, but there was always severe vomiting. He remarked that the vomiting often did not start until 12 or 18 hours after exposure. His comparison of his sensations with those experienced during the induction of anaesthesia recalls that in 1879 a British Medical Association Committee on Anaesthetics studied the possibility of using methyl chloride as an anaesthetic and noted the mild narcotic effect of an alcoholic solution. 'Somnoform', an anaesthetic containing 16 per cent. of methyl chloride, was at one time used in America, and Henderson (1930) has pointed out the dangers of this preparation.

Case 3. F. A. C., a refrigerator engineer, aged 42 years. He had repaired methyl chloride refrigerators for 15 years, and first suffered ill effects in 1929. He had twice had severe symptoms. On one occasion he was repairing a refrigerator in a poorly ventilated room of about 500 cubic ft. capacity when 40 lb. of methyl chloride escaped. He felt dizzy almost at once, had difficulty in walking without stumbling, and in about 10 min. his head started to ache. It was not until about six hours after exposure that he vomited, but the vomiting was then violent and repeated. He became drowsy and slept heavily for the first three nights. The next day he vomited frequently and had severe abdominal pain. His vision became blurred and he noticed diplopia. The headache, eye symptoms, severe vomiting, and abdominal pain persisted for a week. During the second week he vomited occasionally and had periods of drowsiness and difficulty in walking. During the third week he felt tired and unwell, but had no other symptoms. He was off work for three weeks.

Case 4. R. W. H., a refrigerator engineer, aged 34 years. He had worked with methyl chloride for 10 years and had twice had severe symptoms. On one occasion 10 lb. of liquid methyl chloride escaped in a cellar of about 1,500 cubic ft. capacity, ventilated only by a small flap. About 15 min. later he noticed dizziness and a slight headache, found it difficult to walk, and vomited once. He became drowsy about two hours later and slept intermittently for two days, being awakened from time to time by bouts of severe vomiting. His headache disappeared within 24 hours, but ataxia and vomiting persisted for four days. About 24 hours after exposure his vision became misty and he noticed diplopia. The blurred vision and diplopia persisted intermittently for two months, but apart from these features and general malaise he was free from symptoms from the fourth day. He was off duty for a week. The persistence of diplopia illustrates the tendency for isolated symptoms to remain long after otherwise complete recovery.

Case 5. F. B., a refrigerator engineer, aged 33 years. Ten years ago this man had begun his present work, and two years later had developed symptoms for the first time. He remembered two severe attacks and six milder

ones. On 6 June 1940 he was working in a poorly ventilated room, 10 ft. by 8 ft., when 3 lb. of methyl chloride escaped. About five minutes later he felt dizzy and staggered when he tried to walk. Shortly afterwards he developed headache, severe vomiting, and drowsiness which persisted for

TABLE II

Analysis of Cases

Case	Age	Period of work with methyl chloride	Number of attacks	Amount of leak	Type of room	Period off work in most severe attack
1 R.V.	38	6 yr.	1 severe 2 moderate Several mild	—	Cellar	Over 10 months, and residual ataxia
2 R.L.	40	10 yr.	2 moderate 6 or 7 mild	—	Cellar	Light work for one week
3 F.A.C.	42	15 yr.	2 moderate	40 lb.	Little ventilation, 500 cub. ft.	3 weeks
4 R.W.H.	34	10 yr.	2 moderate	10 lb.	Cellar 1500 cub. ft.	1 week
5 F.B.	33	10 yr.	2 moderate 6 mild	3 lb.	Little ventilation, 600 cub. ft.	10 days
6 J.C.S.	36	10 yr.	1 moderate Several mild	50 lb.	Fair ventilation. 900 cub. ft.	4 weeks
7 J.C.	50	10 yr.	1 moderate Several mild	3–4 lb.	Shop	1 week

TABLE III

Analysis of Symptoms of Cases

Symptom	Case 1 R.V.	Case 2 R.L.	Case 3 F.A.C.	Case 4 R.W.H.	Case 5 F.B.	Case 6 J.C.S.	Case 7 J.C.	Total
Ataxia and staggering	+++	++	++	++	++	++	++	7
Nausea and vomiting	+	++	+++	++	++	++	++	7
Headache	+	++	++	+	+	+	++	7
Drowsiness	++	+	+	++	+	+	+	7
Anorexia	++	+	++	+	+	++	+	7
Blurred vision and diplopia	+++	0	++	++	0	+	0	4
Depression	+	0	0	0	0	++	0	2
Abdominal pain	0	0	++	0	0	0	0	1
Spontaneous movements	+++	0	0	0	0	0	0	1
Convulsions	+++	0	0	0	0	0	0	1

+++ Severe ++ Moderately severe + Slight 0 Absent

several days. For the first three nights he was restless and slept badly, but during the day he was drowsy. Ten days later he was fit to start work, but felt unwell and easily tired for several weeks.

Case 6. J. C. S., a refrigerator engineer, aged 36 years. For ten years he had repaired methyl chloride refrigerators, and on several occasions had suffered mild ill effects after exposure to the gas. On one such occasion 50 lb. of liquid methyl chloride escaped in a room of about 900 cubic ft.

capacity with a ventilator 2 ft. square leading to a shaft 10 ft. high. He felt sick and vomited almost immediately, and soon noticed difficulty in walking, mistiness of vision, and drowsiness. These symptoms persisted for three days without intermission. He was off work for four weeks, feeling generally unwell and subject to fits of depression. He had always slept heavily after mild attacks.

Case 7. J. C., refrigerator engineer, aged 50 years. During the ten years he had repaired methyl chloride refrigerators he remembered one severe attack of poisoning and several milder ones. One attack had occurred when he was engaged in repairing an ice-cream mixer in a normally ventilated shop. Most of the work was done with his head in the refrigerator, and owing to a leak 3 or 4 lb. of methyl chloride escaped. Two hours after the leakage he became rather confused and 'dopey', and left the job. It was not until an hour later that he found difficulty in walking, and soon afterwards he vomited and complained of severe headache. He vomited repeatedly for 48 hours. For 72 hours he was drowsy during the day, but sleepless and restless at night. He resumed work seven days after exposure, but for several weeks did not feel fit and was easily tired. This man remarked that his symptoms became more severe some time after the leakage, and attributed the exacerbation to going into fresh air.

The Clinical Syndrome

The cases recorded here and elsewhere may be divided into three groups.

Mild cases. In these cases exposure to the gas is followed by staggering gait, dizziness, and headache after an interval varying from a few minutes to several hours. Sometimes nausea and vomiting occur early and become worse later, but more often they are delayed for several hours or even until the next day. Anorexia is frequent. The patient is rarely prevented from working, and there are no sequelae. Such attacks are common amongst men exposed regularly to methyl chloride.

Moderate cases. Most of the cases described in this paper fall into this group. They differ from the mild attacks by the severity of the symptoms, by their persistence for days or weeks, and by the malaise and weakness which are often present for several weeks. Occasionally there are sequelae; in Case 6 attacks of depression persisted for four weeks, and in Case 4 diplopia and misty vision were present for two months. Vomiting may be severe for a week or more, as in Case 3. Diarrhoea has been described (Kegel, McNally, and Pope, 1929; Sharp, 1930; Porteous, 1930), but it did not occur in the present series. Eye symptoms are common, occurring in about half the cases, and their appearance is usually delayed for 24 hours. They may persist for as long as two months (Case 4). Misty vision is frequent, and seems to be mainly in near sight and associated with difficulty in accommodation. Diplopia is usually intermittent and is probably due to the ataxia and inco-ordination of the extrinsic eye muscles rather than to a definite ocular palsy. Drowsiness occurred in all the cases recorded here and has been widely noted in the literature, but insomnia may also occur either after a period of drowsiness in the early stages (Roth, 1923; Baker,

1927, 1930; Gorham, 1934) or alternating with diurnal drowsiness (Cases 1, 5, and 7). The patients are usually ill for several weeks.

Severe cases. Of the present series, only Case 1 falls into this group, which is characterized by severe involvement of the central nervous system, and often by hepatic and renal damage, and depression of marrow activity. The mortality is considerable, and in those who survive some prolonged or permanent incapacity is not uncommon. Many of the 29 cases described by Kegel, McNally, and Pope (1929) were severe, and 10 of them died.

The nervous system. A striking feature of methyl chloride poisoning is the occurrence of epileptiform convulsions (Schwartz, 1926; Kegel, McNally, and Pope, 1929; Case 1). Convulsions led to death by respiratory failure in all Kegel, McNally, and Pope's fatal cases. Twitching of the limb muscles has been recorded by Baker (1927) and by Kegel, McNally, and Pope (1929), but the spontaneous movements do not appear to have been studied in detail. Several types were seen in Case 1. The most striking was a fine twitching at the rate of two to four per second, which was localized to individual muscles or parts of muscles and produced comparatively little movement of the limb as a whole. These shock-like contractions resembled myoclonic movements, and the eye movements were of this type rather than true nystagmus. Severe action tremor also occurred and persisted until the patient was last seen eight months after exposure to the gas. In addition there were fine contractions of individual muscle fibre bundles which continued for some five weeks; these resembled the fibrillation seen in progressive muscular atrophy. Other indications of damage to the nervous system are common. Ptosis has been recorded by Baker (1927) and by Kegel, McNally, and Pope (1929), and strabismus by the latter authors. In Case 1 bilateral ptosis and diplopia were present, although there was no definite strabismus or ocular palsy, apart from inability to reach full lateral deviation to both sides. Optic atrophy has not been recorded. Slurred speech was noted in two cases by Dorello (1938); in Case 1 it was at times impossible to recognize a single word the patient said. Amnesia was a feature of Case 1, and it has been noticed also by Kegel, McNally, and Pope (1929) and by Dorello (1938). The alternating delirium and drowsiness in Case 1 do not appear to have been recorded previously, though Gimlette (1939) refers to episodes of drowsiness and nightmares in Dorello's cases. The variations of blood-pressure in Case 1 appeared to be due to the changes from drowsiness to restlessness. The cerebrospinal fluid was examined in five of the cases recorded by Baker (1927) and found to be normal. In several of Kegel, McNally, and Pope's (1929) cases the cell count was normal, although in one case the fluid was described as cloudy; in 60 per cent. the pressure was raised. In Case 1 the cerebrospinal fluid was twice examined and found to be chemically and cytologically normal, although the pressure was unusually low.

The liver. Laevulose tolerance tests have not, so far as we know, previously been carried out in methyl chloride poisoning, but it is reasonable to expect

liver damage, since methyl chloride is a chlorinated hydrocarbon. In Case 1 the results suggest impairment of liver function which returned to normal later (Table I). A Takata-Ara test was normal on the tenth day, and there was then no increase in urinary urobilinogen. As Chalmers, Gillam, and Kench (1940) point out, coproporphyrin III has been found in the urine in many cases of liver dysfunction, and the large amounts in the urine of Case 1 may have been due to liver damage. Post-mortem evidence in man (Kegel, McNally, and Pope, 1929) and animals (Sayers, Yant, Thomas, and Berges, 1929) establishes the fact that liver damage can occur in methyl chloride poisoning.

The kidneys. Transient renal damage was recorded by Kegel, McNally, and Pope (1929), who found albumin in the urine in 50 per cent. of cases, casts in 75 per cent., and red cells in 50 per cent. In Case 1 albumin and red cells in the urine and a raised blood-urea suggested some renal damage, but this was transient, for both urine and blood-urea were normal by the sixth day. Anuria is said to occur in most of the severe cases (Kegel, McNally, and Pope, 1929).

The blood. In many of Kegel, McNally, and Pope's cases blood counts showed a leucocytosis and some degree of hypochromic anaemia; neither was found in Case 1, and sternal puncture gave no definite evidence of depression of marrow activity.

Sequelae. Kegel, McNally, and Pope (1929) noted sequelae such as ataxia, ocular symptoms, headache, drowsiness, and amnesia. In this series we found ataxia persisting for at least eight months, depression for four weeks, and misty vision with diplopia lasting two months.

Diagnosis

The diagnosis of methyl chloride poisoning rests chiefly on the history of exposure to the gas and the recognition of the characteristic clinical syndrome, for laboratory investigations give little aid. In cases such as those recorded in this paper, diagnosis is made easy by a history of exposure which is readily obtained, but where a slow leakage occurs from a domestic refrigerator it is possible that the patient and his relatives may be unaware of it, for methyl chloride is almost odourless. Most of Kegel, McNally, and Pope's cases which occurred in private houses were at first diagnosed as food poisoning. Even if a history of exposure to methyl chloride is obtained, unfamiliarity with the clinical syndrome may lead to an incorrect diagnosis. Thus Dorello (1938) attributed 39 cases of illness in an Italian submarine to carbon monoxide poisoning, although he knew that the ship's methyl chloride refrigerators were leaking. He excluded methyl chloride because he thought the concentration could not be sufficient and because the symptoms seemed to him to be atypical and unrelieved when the victims were brought into fresh air. Yet his clinical description was so characteristic that Gimlette (1939) could confidently ascribe these cases to methyl chloride poisoning, and Dorello's misconception that the symptoms rapidly disappear in fresh air is

repeatedly refuted in the literature (Gerbis, 1914; Roth, 1923; Schwartz, 1926; Baker, 1927; Kegel, McNally, and Pope, 1929; Gorham, 1934). Indeed, Kegel, McNally, and Pope regarded the progressive appearance of symptoms after removal from the gas as an important diagnostic feature. This is well illustrated in the present group of cases; in Case 1 it was not

TABLE IV

Urinary Formic Acid in Methyl Chloride Poisoning

Author	Cases	Observation	Amount in mg. per 100 c.c.	Method of estimation
Baker (1927)	21 mild cases	Amount proportional to symptoms	Not stated	Not stated
Baker (1930)	75 mild cases	Found in most cases	Not stated	Not stated
Kegel, McNally, and Pope (1929)	29 severe cases	Found in three cases	6·8 and 9·8	Not stated
		Estimated in two		
Weinstein (1937)	2 cases (1 severe)	Estimated in both cases	1·9 and 2·5	Not stated

Average recorded excretion in methyl chloride poisoning: 5·4 mg. per 100 c.c.

TABLE V

Normal Urinary Formic Acid by Autenrieth's Method

Specimen	24-hour urine volume in c.c.	Formic acid per 100 c.c. in mg.	Formic acid excretion per diem in mg.
1	450	4·7	21·2
2	1200	3·3	39·6
3	1310	8·1	106·1
4	1710	5·2	88·9
5	1170	4·9	57·3

Average normal formic acid excretion: 5·2 mg. per 100 c.c. 62·6 mg. per diem.

until the third day that epileptiform convulsions appeared, and in most of the milder cases symptoms appeared progressively for many hours after removal from the gas. This clinical observation is confirmed experimentally by the work of Sayers, Yant, Thomas, and Berges (1929), who noticed a delayed action when guinea-pigs were exposed to methyl chloride.

Urinary formic acid. Baker (1927) believed that formic acid was excreted in the urine in methyl chloride poisoning, and suggested that its detection was a valuable diagnostic test. He found that it was present in the urine of his patients and absent in controls. He stated that it could be detected before the first symptoms appeared, and that the amount was proportional to the severity of the symptoms. This test has since been widely quoted as an aid to diagnosis (Kegel, McNally, and Pope, 1929; Baker, 1930; Gorham, 1934; Birch, 1935; Weinstein, 1937), and estimations of excreted formic acid have been made by Kegel, McNally, and Pope (1929) and Weinstein (1937). These observations are summarized in Table IV. According to Autenrieth (1919), formic acid is a constituent of normal urine, and he stated that the average amount excreted in 24 hours was 251 mg. This is considerably more than the recorded amounts in methyl chloride poisoning, and

it was therefore decided to repeat Autenrieth's observations, using his method. The results are recorded in Table V. The method is laborious, for an estimation takes about six days. The preliminary estimations recorded indicate that, using Autenrieth's method, the normal daily excretion of urinary formic acid is 20 to 110 mg. It is difficult to compare this result with the figures recorded in Table IV, for neither the method of estimation nor the daily output is recorded in any of these results, but there is no significant difference in the concentration of excreted formic acid. The mere detection of formic acid in the urine is not of diagnostic value in methyl chloride poisoning.

Treatment

Baker (1927) believed that the administration of alkalis helped to alleviate symptoms, and Chalmers, Gillam, and Kench (1940) suggest that acid products liberated by detoxication of methyl chloride may reduce the alkali reserve of the blood. Yet of Baker's (1927) 21 cases, 18 passed alkaline urine, and in Case 1 of our series the carbon dioxide combining power of the plasma was 53 volumes per cent. before alkalis were given, but Weinstein (1937) recorded a case in which the carbon dioxide combining power of the plasma was 37 volumes per cent. and later rose to 50 volumes per cent. Methyl chloride is a chlorinated hydrocarbon, and this group of substances is particularly prone to cause liver damage; it is therefore advisable to attempt to protect the liver by a liberal allowance of glucose. For the same reason, if sedatives are necessary to control convulsions or to induce sleep, substances such as chloral hydrate and chloroform should be avoided.

Prevention

In America, methyl chloride is widely used as a refrigerant; Kegel, McNally, and Pope (1930) state that 75,000 methyl chloride refrigerators were in use in Chicago in 1928. During that year they saw 29 severe cases of poisoning, with 10 deaths. This situation naturally gave rise to anxiety and led the American Medical Association Committee on Poisonous Gases to emphasize the dangers of methyl chloride in their report on *Household Mechanical Refrigeration* (McCord, 1930). Since that time methods of protection against this substance have been much discussed in America. The problem has so far attracted little attention in this country, but our increasing use of methyl chloride necessitates serious consideration of its dangers and of the methods available to minimize them. Although methyl chloride can cause serious and even fatal illness, yet it has only a faint odour and it is non-irritating to the eyes and the respiratory mucous membrane. This makes it difficult to detect leakage and allows repair work to be carried out in a considerable concentration of the gas, particularly as the onset of symptoms is sometimes delayed for several hours. Exposure to the gas occurs, as a rule, in one of three ways:

By leakage in factories manufacturing refrigerators (Baker, 1927; Kegel, McNally, and Pope, 1929).

By leakage during repairs to refrigerators (Bridge, 1931; Bireh, 1935; Weinstein, 1937).

By leakage from refrigerators in use (Kegel, McNally, and Pope, 1929).

Somewhat different methods of protection are required in each of these circumstances, but adequate ventilation is of importance in all. This is illustrated by Baker's (1927) cases in which exposure occurred because, after testing evaporators in a refrigerator factory, it was the practice to blow the used methyl chloride into the workshop. It was found that many fewer cases occurred in the summer, when the windows were open, and an adequate exhaust system proved effective in preventing ill effects. The protection of repairers is a difficult problem, and Baker (1930) believed that they were exposed to the most serious risk. Leakage of large amounts of gas seems inevitable in this work, and little attempt is made to avoid exposure. Much of the danger could be avoided if the repairer would leave the room for a time when a 'blow-out' occurred, but it is difficult to convince these men that an inodorous gas can be dangerous. The ideal method of protection is one independent of the co-operation of the workman; as Legge (1934) wrote in his second axiom: 'If you can bring an influence to bear external to the workman (i.e. one over which he can exercise no control), you will be successful; if you cannot or do not, you will never be wholly successful.' Even if the repairer could be provided with an efficient respirator, there is no guarantee that he would use it.

Leakage from methyl chloride refrigerators in use generally passes unnoticed until the apparatus fails to work owing to the loss of its charge of refrigerant. The difficulty of preventing and detecting such leaks was appreciated by Connolly, Claffey, and Aeberly (1930), who suggested that the greatest safety would be attained by placing the refrigerating system in a gas-tight container ventilated to the outside air. Even a slow, unnoticed leak may be dangerous, for Roth (1923) and Baker (1930) have maintained that repeated small doses of methyl chloride produce a cumulative effect, and rapid leakage from domestic refrigerators has caused some of the most severe cases of poisoning yet recorded. Of Kegel, McNally, and Pope's 29 severe cases 26, including all 10 fatal cases, occurred in this way. The severity of the symptoms and the high mortality were due to the dangerous system of refrigeration used; the refrigerators were in flats and connected to a common multiple unit refrigerating plant containing several hundred pounds of methyl chloride under 100 lb. to the sq. in. pressure. A leak from any part of this system allowed a large amount of gas to escape rapidly under high pressure. The dangers of such multiple systems have been stressed by McCord (1930), who discussed the design of refrigerating plants and the measures which could be taken to minimize the risk of leakage. Adequate ventilation will minimize the danger of slow leakage, but rapid leakage from a multiple system has led to fatal poisoning in rooms with open windows (Kegel, McNally, and Pope, 1929). Even if the risk of leakage is reduced by appreciation of the dangers of multiple systems, and by care in

the design of refrigerators, it will continue to occur at times, either owing to a fault in the refrigerator or in the course of repairs. When such leakage does occur methyl chloride is dangerous, not because it is a powerful poison in low concentrations, but because its inodorous and non-irritating character permits heedless exposure to a considerable concentration of the gas for the prolonged period necessary to cause severe poisoning. For this reason the addition of a detector substance has been tried in America, where methyl chloride with 1 per cent. acrolein was placed on the market as Methyl Chloride A. The American Medical Association Committee on Poisonous Gases did not approve this substance because it afforded no protection to infants, the infirm, and refrigerator repairers. They maintained that it was more desirable to develop a safe refrigerant than to attempt to minimize the hazards of methyl chloride by devices which could protect only a section of the public. On the other hand, Connolly, Claffey, and Aeberly (1930) believed the discovery of a safe refrigerant to be unlikely, and until such a refrigerant is discovered the advantages of a detector substance are too striking to be overlooked. Its use would draw attention to the dangerous nature of the gas and facilitate the education of those who use it, it would discourage the release of the gas into ill-ventilated workshops, it would make it difficult for the repairer to continue his work in a contaminated atmosphere, and it would warn the householder of a leak from his refrigerator.

A detector substance must fulfil several criteria if it is to be of value:

(1) It should be easily detectable in low concentrations, for instance by smell or by a lachrymatory action.
(2) It should be non-toxic or, at the least, of low toxicity.
(3) It should have physical properties which would enable it to circulate in the refrigerating system.
(4) It should not interfere with the physical properties of methyl chloride which make it a valuable refrigerant.
(5) It should not damage the refrigerating mechanism.
(6) In low concentrations it should not render food unusable.

It must be admitted that a detector substance does not provide an ideal solution of this problem, but the warning it would give is especially valuable in dealing with a gas of this kind, and its introduction would do much to diminish this industrial hazard.

Summary

1. A severe case of methyl chloride poisoning in a refrigerator repairer is fully described.

2. Case histories of attacks of poisoning in six other refrigerator workmen are recorded.

3. The clinical material is analysed and the clinical syndrome of methyl chloride poisoning discussed.

4. The diagnosis is discussed and the value of urinary formic acid estimations is assessed.

5. The dangers of methyl chloride as a refrigerant are discussed and methods of prevention against exposure considered.

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PREGNANCY AND DIABETES[1]

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Introduction

The use of insulin has greatly reduced the incidence of amenorrhoea and sterility in diabetic women, but it is generally agreed that even well controlled patients are less fertile than normal women of the same age. Many more diabetics become pregnant now, and in recent years it has therefore been possible to make a wider study of the effects of pregnancy on diabetes and of the influence exerted by this disease on the outcome of the pregnancy. Several series of cases have been collected and analysed with special reference to maternal and foetal mortality both in this country and in America, and the results obtained in some of the larger and more important of these are summarized in Table I. If the results of the pre-insulin series are compared with those obtained since the introduction of insulin therapy, it will be seen that while insulin has reduced the maternal mortality to an almost negligible figure the same cannot be said of the foetal mortality, which has remained by contrast remarkably high. The reduction of foetal and neonatal mortality constitutes the chief problem in the management of diabetic pregnancies, and the main theories put forward to account for this heavy mortality will now be considered.

It is generally agreed that if a pregnant diabetic is allowed to go to term without special supervision either the baby tends to be over-sized and is often stillborn or, should a live child be delivered, death within 24 to 48 hours of delivery is not uncommon, no obvious cause being present. The incidence of 'giant' babies in diabetic pregnancies has usually been attributed directly to excessive supplies of sugar reaching the foetus as a result of maternal hyperglycaemia. We agree with this view and are sure that the foetus must utilize an increased amount of sugar because we have sometimes found the maternal glycaemia much higher than the foetal, such figures as 180 and 80 mg. per 100 c.c. having been found at birth. Recently the importance of the role played by the pituitary in diabetes has become increasingly stressed, and it has been suggested that the overgrowth may be due to an excess of growth hormone. This latter view receives support from the independent experiments of Snyder (1934) and of Hoopes (1933) who injected prolan into pregnant rats and rabbits and produced abortion and stillbirth with over-development and maceration of the 'giant' foetus. Clinically, White, Titus, Joslin, and Hunt (1939) observed that the weight of the babies in

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died probably 24 hours before operation (Case 25). This almost negligible maternal mortality is characteristic of most of the recent series of cases reported, and is in marked contrast to our foetal mortality rate which also approximates closely to the best figures obtained by other workers. Out of a total of 57 babies 21 were either born dead or failed to survive more than a few hours, giving a mortality rate of 37 per cent. Analysis of the foetal deaths shows that five were due to abortions of which three were therapeutic and carried out only because the mother did not wish to go through with another pregnancy; if these three are excluded the foetal mortality rate is reduced to 33 per cent.

In order to discover the effect of treatment and control of the maternal diabetes on the outcome of the pregnancy our series has been divided into three groups according to whether supervision was complete, partial, or nil, the results being included with the total mortality figures in Table II. The term 'complete supervision' implies that the mother was seen at regular intervals, and her treatment adjusted throughout the pregnancy, if necessary, by admission to hospital or a nursing home for such treatment and for delivery of the baby. Under 'partial supervision' are included those cases which were seen either at irregular intervals or, more commonly, only during the later stages of pregnancy. Pregnancies in which the patient was admitted in labour or delivered at home without having been seen at all or more than very occasionally by us during the pregnancy were included under the heading of 'no supervision'. Subdivision into the three groups described above shows the foetal mortality rate to be 28, 50, and 70 per cent. respectively, the rate in the first or 'complete supervision' group being further reduced to 23 per cent. if therapeutic abortions are excluded. These figures agree closely with those of Skipper (1933) and provide strong evidence in favour of the view that maximum control of the maternal diabetes during pregnancy and delivery constitutes one, if not the most important, factor in the reduction of foetal mortality.

Detailed Observations

The effect of pregnancy on the maternal diabetes has been studied in detail in 54 pregnancies of our series, and the findings are summarized in the Appendix. Special attention has been paid to the duration of the diabetes, the influence of pregnancy on the insulin requirement, the presence or absence of ketosis, and the renal threshold for sugar.

Duration of diabetes. In eight patients the diabetes was first discovered during the pregnancy, while in the remaining 36 the disease was known to have been present from 1 to 19 years before the onset of pregnancy, no less than nine cases having been diabetic for 10 years or more. Of the eight cases discovered during pregnancy five were primiparae, the remaining three having had one or two previous pregnancies.

Influence of pregnancy on insulin requirements. In studying the effect of pregnancy on the maternal diabetes it was found that in 38 pregnancies the mother was taking insulin when she became pregnant, and that in 13

pregnancies this was not the case, either because the diabetes was not diagnosed until after pregnancy began or because the disease was very mild; details on this point in the three remaining pregnancies could not be obtained. In 16 of the 38 pregnancies the insulin requirement remained unchanged during the first trimester, in 13 there was a rise of not more than 10 units per diem, while in five there was a fall of the same small order; in four cases information was not available. By the end of the second trimester the insulin exceeded the pre-pregnancy dose in 20 pregnancies, was the same in 11, and had fallen slightly in four; in three cases dosage was not recorded. During the third trimester the number of pregnancies in which the insulin requirement increased rose to 26, eight showing no change and three a fall, one only being in doubt on account of insufficient data.

Of the 13 pregnancies which occurred in patients not taking insulin, in eight diabetes was first diagnosed during the pregnancy, the remaining five being in mild cases of one to five years' standing. Only two of these patients were found to require insulin by the end of the first trimester, the diabetes at this stage of the pregnancy being either controlled by diet or not yet manifest in the other 11 instances. By the end of the second trimester, however, the disease had been diagnosed in every case; seven still required no insulin, four were taking from 18 to 76 units daily, and in two the date at which insulin was started could not be ascertained. At the time of delivery nine of the 13 required insulin, the dosage being 10 units per diem or less in two, and three were controlled throughout by diet alone; the evidence in the thirteenth case was inconclusive.

The increase in insulin dosage during the latter half of pregnancy was often considerable and, although the carbohydrate content of the diet was also often raised in the later months of pregnancy in order to make up for sugar lost as a result of a lowered renal threshold, there can be no doubt that carbohydrate tolerance was diminished in many of our cases during this period, and this agrees with Hurwitz and Irving's (1937) findings for the third trimester. Table III shows the initial and final doses of insulin together with the percentage increase in the five cases which showed the greatest loss of tolerance during pregnancy.

TABLE III

Increase in Insulin Dosage During Pregnancy

Case No.	Initial dose in units	Final dose in units	Percentage increase
10	28	72	157
14	52	128	146
17	32	98	206
19	30	111	270
21	14	72	414

It is generally agreed that delivery, either spontaneous or by Caesarean section, is often followed by an immediate fall in insulin requirement. This was observed in 30 (56 per cent.) of our series of pregnancies, two only requiring an increase of insulin, which in both amounted to less than 10 units,

while in 12 the insulin before and after delivery was unchanged. It was not possible to draw any conclusions on this point in the remaining nine pregnancies, either because the amount of insulin required immediately before delivery was very variable, or because the condition of the patient after delivery made it desirable to give frequent divided doses. The greatest fall noted in our series was from 66 units before delivery to 0 immediately after; this patient was taking 15 units per diem when she became pregnant, but still required no insulin when seen long after delivery.

The more remote effect of pregnancy on maternal diabetes was studied by comparing the insulin requirement at the time of conception with that some months or years later, the length of time necessarily depending upon the frequency with which the patient came up for observation. In 21 pregnancies there was no change in the severity of the diabetes, as indicated by insulin requirement, in the same number the disease was found to be more severe, while in three the insulin had been reduced. In eight cases the amount of insulin being taken long after delivery could not be determined either because a sufficient interval of time had not elapsed or because contact could not be made with the patient. In evaluating these results it is important to remember that diabetes is often a progressive disease and, therefore, in any series of young diabetics there is likely to be an increase in insulin requirement over a period of years, or even months, when the condition is of recent origin.

Ketosis. Severe ketosis is a common complication during pregnancy, being due to loss of carbohydrate tolerance, vomiting, and excessive glycosuria resulting from lowering of the renal threshold, or a combination of these factors. Vomiting usually occurs early in pregnancy and is less important than the other two factors, which tend to combine in the production of attacks of severe ketosis during the later months of pregnancy. Quantitative estimations of ketone bodies were not carried out, but routine examination of the urine by Rothera's and Gerhardt's tests enabled our series of pregnancies to be divided into three groups according to whether ketosis was absent, present but not severe, or severe. In 11 instances ketosis was absent throughout, in 16 ketosis was present at some time during the pregnancy but was never severe, and in 18 severe ketosis was present, although only for short periods; no record of ketosis could be obtained in the remaining 9 pregnancies. Attacks of severe ketosis were most common during or after the fifth month, and in 17 out of the 18 pregnancies in which they occurred the patients also had a lowered renal threshold, which produced such a heavy glycosuria, even when the blood-sugar was kept as low as possible with insulin, that the resulting low utilization of carbohydrate made ketosis inevitable. In every case suitable treatment with a higher carbohydrate diet and adequate doses of insulin resulted in the disappearance of the ketosis, and the maternal mortality from this cause was nil, the only maternal death in the series being from pulmonary embolism. As regards the influence, if any, of ketosis on foetal mortality, it was found that

the 18 pregnancies in which it was noted to be severe but of short duration resulted in 13 live babies (one pair of twins), two neonatal deaths, three stillbirths, and one therapeutic abortion, while the 11 in which ketosis was absent throughout the pregnancy gave nine live babies, one neonatal death, and one stillbirth. These figures are too small to allow of any conclusions being drawn, but do not suggest that severe ketosis of short duration is an important factor in foetal mortality.

Renal threshold. The most exact determination of the threshold, or level of blood-sugar at which glycosuria occurs, necessitates the carrying out of a blood-sugar curve, but a fair estimate can be obtained by means of the following technique (Lawrence, 1940). The bladder is emptied as completely as possible and the specimen tested for sugar; 15 min. later blood is taken for estimation of sugar content and, after a further interval of 15 min., a second urine specimen is obtained and tested for sugar. No food is eaten during the ½ hr. of the test. In a reasonably well balanced patient it should be possible to carry out this test when the blood-sugar is likely to be somewhere between 80 and 150 mg. per 100 c.c., and the presence of sugar in the second specimen in these circumstances may be taken to indicate lowering of the renal threshold. The presence of heavy glycosuria in the first specimen has been shown by Lawrence to produce only traces of sugar in the second specimen, provided care has been taken that emptying of the bladder has been as complete as possible. This modified threshold test was performed as a routine in all our cases of pregnancy, and repeated until the level of the threshold had been satisfactorily determined. If with a blood-sugar of 170 to 180 mg. per 100 c.c. or less, the second urine specimen was sugar-free, the threshold was considered as normal; if it contained more than slight traces of sugar, a low threshold was recorded.

In 37 pregnancies the renal threshold was found to be lowered, in four of which sugar was passed in large quantities at blood-sugar levels of less than 100 mg. per 100 c.c.; in 13 cases the test gave doubtful results, while in only four did the threshold appear to be normal. The earliest date at which this lowering of threshold was observed in our series was the second month, while the latest was the eighth, the most common time of appearance being between the fourth and sixth months. These findings agree well with those of other observers, and there can be no doubt that pregnancy produces a definite lowering, amounting in some cases to an almost complete loss, of renal threshold in diabetic women, as it does commonly in normal pregnant women. The importance of this has already been discussed under the heading of ketosis, and will be referred to again in the discussion on the management of pregnancy in diabetes.

Abnormal Features of Pregnancy in Diabetics

Maternal.

Toxaemia. Reference has already been made to the view that toxaemia of pregnancy is more common in diabetic than in normal women, and to

the possible association of this with the high foetal mortality. Severe grades of toxaemia with eclamptic or pre-eclamptic manifestations offer no difficulty in diagnosis, but were not seen in any of our series of pregnancies. Milder forms of toxaemia in which albuminuria, hypertension, and oedema are the chief signs, are less easily diagnosed in diabetics, on account of the fact that albuminuria and slight oedema are sometimes seen in diabetes uncomplicated by pregnancy, and oedema alone is a common enough finding in the later months of normal pregnancies. For this reason toxaemia was diagnosed only when all three signs were present, special importance being attached to hypertension. Albuminuria in appreciable quantity was present in nine cases, in four of which it was heavy at some period during the pregnancy. A rise in systolic blood-pressure to 140 mm. or over was recorded in seven pregnancies and was associated with albuminuria in five, but many records of blood-pressure were lacking. Oedema of a degree not ordinarily found in uncomplicated pregnancies was observed in 12 instances, being associated with albuminuria in seven, and with albuminuria and hypertension in five. Thus only five pregnancies showed all three signs and were therefore diagnosed as toxaemic, one (in Case 26) being complicated in addition by gross oedema of the nephrotic type, granular and hyaline casts in the urine, marked impairment of renal function, and severe anaemia. These five toxaemic pregnancies, treated by rest, fluids, and low protein diet, resulted in the birth of six live babies (one twin pregnancy) without any maternal mortality, and do not therefore lend support to the recent American view that toxaemia of pregnancy is an important factor in foetal mortality. We have not undertaken any oestrin or prolan analyses in our cases as we have been assured by experts that such analyses are so uncertain and variable as to have no clear significance.

Hydramnios. Before the introduction of insulin therapy, hydramnios was relatively common in diabetic pregnancies (Williams, 1909), but recently its incidence is said to have fallen, the condition now being held to occur only in uncontrolled cases. The diagnosis of hydramnios is difficult because the amount of liquor amnii varies within wide limits in normal pregnancies, being related to the size of the foetus, the presence or absence of foetal abnormalities, and other factors, including toxaemia of pregnancy. For this reason hydramnios has been diagnosed in the present series of pregnancies only when the liquor amnii was grossly in excess of normal, pregnancies in which there seemed to be only moderate or slight excess being recorded as doubtful. On this definition hydramnios was diagnosed in five pregnancies, a further 15 showing some excess of liquor amnii and being therefore included under the heading of doubtful hydramnios. Of the five true cases, one (Case 8) developed acute hydramnios at the 24th week with spontaneous rupture of the membranes and abortion, while in another (Case 20) the pregnancy was terminated by hysterotomy at the 26th week. Two of the remaining three pregnancies resulted in stillborn babies, one of which (in Case 40) weighed 12 lb. and died from a tentorial tear during delivery, and

the third patient was delivered of a live child by Caesarean section during labour. The 15 pregnancies with 'doubtful hydramnios' included two twin pregnancies and two with toxaemic manifestations, and resulted in 15 live babies, one dead macerated foetus of 5 lb. delivered naturally, and one abortion at the sixth month. The control of the diabetes in the five pregnancies with gross excess of liquor amnii was satisfactory in three, two being in very mild cases and requiring no insulin, and unsatisfactory in two patients, of whom one received no supervision, while the other (Case 44), from whom a live baby was obtained, was extremely difficult to balance on account of the severity of her diabetes.

Foetal.

Size. If the five abortions are excluded, the remaining 49 pregnancies resulted in the birth of 52 babies of which the birth-weight was determined in 45 instances. This was found to be 9 lb. or more in 27, of which seven weighed between 10 and 11 lb., and six equalled or exceeded 11 lb., the heaviest weighing as much as 12 lb. 6 oz. The maximum, minimum, and average weights are shown, together with the foetal mortality and mode of delivery, in Table IV.

TABLE IV

Relation of Mode of Delivery, Weight, and Foetal Mortality

Mode of delivery	Live babies, weight in lb. and oz.				Stillbirths and neonatal deaths, weight, in lb. and oz.			
	Number	Maximum	Minimum	Average	Number	Maximum	Minimum	Average
Caesarean section	23	11 11	6 5	8 8	4	11 0	5 8	7 14
Spontaneous	11	11 0	5 8	7 11	5	12 6	5 0	8 4
Induction	2	9 12	8 2	8 15	0	—	—	—
Totals	36	11 11	5 8	8 6	9	12 6	5 0	8 1

From these figures it appears that there is little or no relation between the weight of the foetus and its chance of survival, the maximum, minimum, and average figures for live babies and foetal deaths being almost identical. It must, however, be said that one baby delivered by Caesarean section was of unknown weight, but was noted to be of average size, while four babies of unknown weight resulted from spontaneous delivery, all of which were stillborn; the number of inductions is obviously too small to allow of any conclusions being drawn.

With two exceptions, all the pregnancies in which Caesarean section was performed were completely supervised, and the influence of maternal hyperglycaemia, if any, on the size of the foetus eliminated as far as possible by careful control of the diabetes, but this was not the case in those pregnancies in which spontaneous delivery occurred, and it is therefore interesting to note the relationship in these pregnancies between the weight of the foetus and the degree of supervision of the maternal diabetes (Table V).

TABLE V

Relation between Weight of Baby and Degree of Supervision in Spontaneous Deliveries

Supervision	Number	Weight, in lb. and oz.		
		Maximum	Minimum	Average
Complete	7	8 8	6 1	6 15
Partial	3	6 0	5 0	5 8
None	6	12 6	8 9	10 2

These figures support the view widely held, and expressed at the beginning of this paper, that uncontrolled diabetics, if allowed to go to term, tend to produce 'giant' babies.

Early maturity. Caesarean section was carried out 23 times in the present series of cases and, with one or two exceptions, was performed between the 36th and 38th week according to the calculations of our obstetric colleagues. In spite of this premature delivery, the average weight of the babies so born will be seen from Table IV to have been 8 lb. 8 oz. Moreover, careful examination of these babies showed that, in addition to their weight being well up to or even in excess of normal, although delivered from two to four weeks before term, many had reached maturity. This conclusion was based largely on the general appearance of the baby and the degree of development of the nails, and was supported by the gynaecologist who performed the Caesarean sections. It happened far too frequently to be explained by mistakes in menstrual dates. Although the large size of these babies has received frequent comment, their early maturity does not seem to have received previous notice. If our observations are correct and some of these babies are mature at the 37th week, then by the 40th week they would be three to four weeks post-mature, less viable like all over-mature babies, which might account for the large number of stillbirths known to occur when diabetic pregnancies go on to full term. This was actually observed in our series, seven out of 19 babies delivered spontaneously being stillborn (see Table VI).

Congenital abnormalities. At the beginning of the present paper congenital abnormalities were included as one of the causes contributory to the high foetal mortality in diabetic pregnancies. In the present series only two possible instances of this were observed, in one of which, congenital morbus cordis, the signs did not persist after the first few weeks of life, while in the other, pulmonary atelectasis, the condition proved fatal 10 hours after delivery by Caesarean section.

Influence of Mode and Time of Delivery on Results

The results of Caesarean section, spontaneous delivery, and induction are summarized in Table VI, from which it will be seen that while 23 live babies were obtained from 27 pregnancies subjected to Caesarean section, only 11 live babies resulted from 19 pregnancies terminating in spontaneous delivery; only three births were induced and no conclusions can therefore be drawn.

TABLE VI

Mode of Delivery and Foetal Mortality

Mode of delivery	Total pregnancies	Live babies	Dead babies	
			Stillborn	Neonatal
Caesarean section	27	23 (1 pair of twins)	2	3
Spontaneous	19	11 (1 pair of twins)	8 (1 pair of twins)	2
Induction	3	2	1	0
Total	49	36	11	5

Analysis of the five foetal deaths after Caesarean section shows that three occurred in pregnancies with complete, one with partial, and one with no supervision. In two of the three completely supervised pregnancies a stillborn foetus resulted from allowing the pregnancy to go on too long, operation being performed in one instance at full term and in the other at the 38th week. The latter case was particularly unfortunate and instructive in that the foetus was alive on the day on which the operation was first planned to take place, but died during the following few days while treatment for scabies was being carried out in order to minimize the risk of infection. The third death in this group took place three hours after Caesarean section, no cause being discovered. The patient with partial supervision was admitted in labour with ruptured membranes, and the foetus died from atelectasis 10 hours after operation. The last foetal death followed Caesarean section on a patient whose diabetes was never controlled, and resulted from blue asphyxia 24 hours after operation, the foetal brain at autopsy showing oedema and haemorrhages. It is probable, therefore, that both stillbirths could have been avoided by earlier operation, and the foetal death in the last case might also possibly have been prevented by adequate supervision of the maternal diabetes.

If the results of spontaneous delivery are examined it will be seen that 19 pregnancies gave 11 living and nine dead babies, of which seven were stillborn and two died shortly after delivery. Before arriving at any conclusions about the relative merits of Caesarean section and spontaneous delivery in diabetic pregnancies it is necessary to take into consideration the

TABLE VII

Effect of Supervision on Results of Spontaneous Delivery

Degree of supervision	Live babies	Stillbirths	Neonatal deaths
Complete	6	1	1
Partial	2	1	0
None	3	5	1

degree of supervision of the maternal diabetes, which varied greatly in the two groups of pregnancies in the present series. Out of a total of 27 pregnancies terminating in Caesarean section, 25 were completely supervised, while only seven out of 19 pregnancies with spontaneous delivery fell into this category, three receiving partial supervision, and nine no supervision. For this reason the relationship between the degree of supervision and the

result of the pregnancy was investigated in the cases spontaneously delivered and the findings summarized in Table VII.

While these figures are too small to permit of definite conclusions being drawn, they suggest the influence of control of the maternal diabetes on the result of the pregnancies allowed to go to term, and at the same time show that, even in the completely supervised pregnancies of our series, the foetal survival rate was appreciably lower when spontaneous delivery occurred than when Caesarean section was performed between the 36th and 38th weeks of gestation, six live babies out of eight being obtained by the former mode of delivery and 23 out of 25 by the latter. Induction was carried out in only three pregnancies, all of which were in completely supervised patients, and resulted in two live babies, and one stillbirth due to torsion of the cord at the 31st week.

Breast-feeding

It is generally agreed that in diabetic mothers the secretion of milk is frequently deficient, and that comparatively few are able successfully to breast-feed their babies for the normal length of time. In the present series breast-feeding was attempted in all those cases delivered under our care in which such contra-indications as severe loss of control of the diabetes or anaemia were absent. In order to allow for loss of carbohydrate by lactation the diet in most cases contained about 200 gm. of carbohydrate and included adequate quantities of milk and vitamins. Under these conditions breast-feeding was noted to have been successful in 11 instances, in six of which the supply of milk was plentiful, while in the remaining five it fell off after the first few weeks or months. In one case in which the mother gave birth to twins by spontaneous delivery both babies were successfully breast-fed. It is noteworthy that all these patients were completely supervised throughout their pregnancies. It is possible that some of the babies not delivered under our care, and therefore not completely supervised, were also breast-fed with partial or complete success, but details of these few cases were not available.

The Advisability of Pregnancy in Diabetes

It may be useful to mention the grounds on which, in any particular case, we decide whether pregnancy is to be encouraged or prevented. Our views are based partly on the hereditary aspect, but much more on the human aspects of the mother's temperament, situation, and wishes.

Heredity. It is clear that a hereditary factor exists in diabetes, very marked in some families, but we do not agree with the current theory put forward by Pincus and White (1933) that it is transmitted as a Mendelian recessive characteristic or that the likelihood of transmission can be predicted by Mendelian rules. We always investigate the family history of both husband and wife and, if a history of diabetes is found, especially in both, point out the risk of diabetes developing in the children some time in life (although we believe that there is no record to date of such children developing diabetes), and would consider a bad family history of diabetes on

either side an important reason for advising against pregnancy or for terminating an early pregnancy. The most important deciding factor which influences us in an otherwise healthy diabetic woman is her strong wish for a child, and her determination, knowing the difficulties, to co-operate in every way. Should she already have two or three children, we have been almost without exception opposed to a further pregnancy, but if a marriage is unhappily childless, and the patient is willing and able to co-operate fully, consenting to Caesarean section if necessary, we encourage such a pregnancy and gladly undertake its supervision. In patients, on the other hand, who are unwilling, or by reason of carelessness or stupidity unable, to co-operate we think it right to discourage pregnancy and, should it occur, usually advise therapeutic abortion and sterilization then or later. If such a pregnancy is discovered later, say at the fourth to six months, we are against interruption, as the procedure may then be as difficult as delivery in due course. The duration and severity of uncomplicated diabetes makes less difference, we think, to the outcome than the possibility of good control throughout the pregnancy. We may state, to illustrate our point of view, that we are inclined to discourage diabetic pregnancies in war time, as the possibility of adequate supervision, at least in London, is so uncertain.

Practical Management

The management of diabetes presents special difficulties during pregnancy which demand close supervision of the patient. From the maternal point of view ketosis and hypoglycaemia must be avoided, which would present no special difficulty were it not for the simultaneous necessity of controlling hyperglycaemia more closely than usual with the aim of preventing harmful over-development of the foetus. This and the changing metabolism demand frequent supervision if full control is to be maintained; our patients are therefore advised to attend every four weeks for the first six months and every two weeks in the last trimester. At each visit at least two samples of urine are tested qualitatively for sugar, acetone, and albumen, the blood-sugar is estimated, and a threshold test undertaken. The blood-pressure is taken and the obstetrical condition checked by a visit to the obstetrician of the Ante-natal Department. If progress is unsatisfactory and especially if heavy ketosis is present and persists under modifications of out-patient treatment, we admit the patient for a short period of therapeutic observation and find this the only way of tackling such problems. The majority, however, have not required in-patient treatment prior to delivery.

In the early months we have to make little change in the pre-pregnancy treatment. Our diets usually remain at 150 gm. carbohydrate, but we ensure an adequate supply of vitamins and mineral salts, especially calcium and iron, by adding milk and iron to the diet if necessary. As a rule the insulin also requires little modification and we continue either two doses of soluble insulin, morning and evening, or, more often, one morning dose of protamine insulin aided by some soluble insulin at the same time. We try to control

hyperglycaemia more thoroughly than before and may have to give a few extra units or add protamine insulin to get better control of the blood-sugar by night. Vomiting of pregnancy and ketosis have been inconspicuous and have given no trouble in the early months. Unfortunately, this satisfactory condition seldom persists throughout pregnancy, and a change for the worse usually takes place about the fifth or sixth month, dependent almost entirely on a lowering of the renal threshold. A brief description of a typical case, its investigation, and treatment may be helpful.

At a routine visit at the middle of the fifth month a complete change from the previous findings is at once noticed. At the previous visit the urine contained traces of sugar, but no ketosis, and the blood-sugar four hours after the morning insulin (30 units of protamine zinc insulin and 16 units of soluble insulin) was 120 mg. per 100 c.c., a satisfactory figure. Now the urine is loaded with sugar and ketone bodies, the blood-sugar is essentially the same (130 mg. per 100 c.c.) and the threshold test shows a fall, so that 4 per cent. of glycosuria accompanies this level of blood-sugar. Positive ferric chloride tests show a heavy ketosis and although clinical signs of nausea, &c., are absent, the patient is admitted to hospital. The total sugar excretion per diem is estimated and found to be 90 gm., although the blood-sugar varies between 90 and 200 mg. per 100 c.c. at different times and cannot be lowered without risk of hypoglycaemia. The diet contains 150 gm. of carbohydrate of which 90 gm. are lost in the urine and probably 30 gm. used by the foetus, so that the maternal utilization is only 30 gm., a figure so low as to make heavy ketosis inevitable. This cannot be rectified by giving more insulin (as the heavy glycosuria cannot be prevented) and it is our practice to add to the diet approximately what is lost in the urine. In this case 100 gm. are added (making the diet include 250 gm.) so that, although glycosuria persists, more carbohydrate will be retained and metabolized. At the same time this additional carbohydrate raises the level of hyperglycaemia, and we adjust the insulin at a higher dose to reduce the blood-sugar to the lowest safe figure. At this stage we often give a second dose of insulin before tea or supper to control evening hyperglycaemia and, in the above example, the patient left hospital in a week on 250 gm. of carbohydrate and 40 units of protamine zinc insulin, with 20 units of soluble insulin in the morning and 16 units of soluble insulin before tea, still passing large amounts of sugar, but no ketone bodies, for the remainder of the pregnancy. There is, of course, no real need to estimate the urinary sugar loss, and to combat ketosis 50 gm., and perhaps later 100 gm., of carbohydrate can be added empirically to the diet and the insulin adjusted to cover these additions. For this, blood-sugar estimations are essential, and we usually make our final adjustments of insulin on the result of four blood-sugar estimations which give a picture of the diabetic state throughout the 24 hours, namely fasting, before lunch, at 5.30 p.m. and at 10 p.m.

In our experience the fall in the renal threshold is the cause of other difficulties besides ketosis. It is clear that urine sugar tests under these

conditions are little help in assessing glycaemia, and we can no longer make the usual assumption that if the urine is clear hyperglycaemia is not excessive. Therefore in our effort, which we think important, to prevent high levels of blood-sugar we are dependent on frequent and inconvenient blood-sugar estimations. With this precaution, we raise the insulin dose as high as is necessary to keep the blood-sugar below 200 mg. per 100 c.c., throughout the 24 hours, giving often greatly increased amounts of insulin, and occasionally three doses a day in the last trimester. In such cases we are unable to keep the blood-sugar strictly normal, that is, below 150 mg. per 100 c.c., without hypoglycaemia, and at certain times no doubt 200 mg. per 100 c.c. is inevitably exceeded. We are certain, however, that the more normal the maternal blood-sugar the more live babies are born.

In our experience short periods of ketosis have made no difference to the foetus, but none of our patients has had a really serious ketosis threatening coma.

Hypoglycaemia

Many of our pregnant diabetics have had mild attacks of hypoglycaemia, and in a few these have been severe, involving complete unconsciousness and requiring intravenous glucose for recovery. None seems to have affected the foetus unfavourably. Some mothers have said that attacks of hypoglycaemia stop, but others that they accentuate the baby's movements. Hypoglycaemia is most common in the later months when large doses of insulin are being used to try to control hyperglycaemia, and we know of no means by which they can be entirely eliminated, as they are easily induced by even slight extra exercise and irregular insulin absorption from day to day, but 'buffer' carbohydrate meals prevent them in most cases. Failure to recognize that glycosuria may be due to a low renal threshold may lead to serious hypoglycaemia when a vain attempt is made to make the urine sugar-free by heroic increases in insulin dosage. Occasionally in the last month spontaneous improvement may bring on hypoglycaemia. Labour itself, with the intense muscular activity involved, is another factor which may bring on hypoglycaemia, and it is wise to reduce the previous insulin considerably during labour, but the period at which hypoglycaemia is almost certain to occur, unless the dosage is greatly changed, is immediately after labour when the insulin requirement almost always falls steeply for 24 to 48 hours. This fall was noted in 30 of our series of 54 pregnancies, and is recorded in the appendix. The danger of hypoglycaemia immediately after labour has been stressed by other writers, and all agree that insulin should be drastically reduced in anticipation, and not raised again until hyperglycaemia returns. It is interesting and puzzling that the increased tolerance may occasionally continue for days or weeks. We have seen one patient, who had had 40 units a day for 10 years, stop insulin altogether for six days, although the same diet was maintained, and eight weeks elapsed before she had to return to her full previous dose. The temporary improvement of two other cases was equally clear although less quantitatively striking.

Methods of Delivery

While no hard-and-fast rules can be laid down on the subject of mode of delivery in the pregnant diabetic, each case requiring individual consideration and the application of the method best suited to it, there are certain general indications which must be recognized if a correct choice is to be made. The first is the parity of the patient, primiparae often requiring treatment different from that best suited to multiparae. It is generally unwise, in our opinion, to allow a diabetic in her first pregnancy to be delivered spontaneously at term, especially if there is any evidence that the baby is large. Our reasons for taking this view are that in such cases foetal death in the last month of pregnancy is far from uncommon, and that, should this danger be avoided, the risks involved by a long and difficult labour exceed those attendant upon Caesarean section or early induction. If spontaneous delivery at term is the method generally adopted in these cases, although the causes of stillbirth are obscure, there can be no doubt that death often occurs, and particularly when the maternal diabetes has received little or no attention during the pregnancy. Furthermore, the high incidence of neonatal death among the babies of diabetic mothers is in part, at any rate, due to birth injuries sustained during the difficult and prolonged labour associated with large babies. Unless, therefore, there is good reason to believe that the foetus is of normal size and that labour will not be difficult or prolonged, predictions almost impossible in a first pregnancy, we believe that Caesarean section at the 36th to 38th week offers a better chance of obtaining a live baby than spontaneous delivery at term. This has the further advantages of making it possible not only to arrange that delivery takes place in hospital under the best possible conditions, but also to sterilize the patient, should it be desirable, at the same time. This view is supported by the results obtained in our series of cases and, by adopting this procedure, we have been able on a number of occasions to obtain live babies in patients who gave histories of one or more spontaneously delivered stillborn children.

With multiparae the position is somewhat different, as it is possible to predict an easy labour with greater accuracy, and also to obtain useful information from what has occurred in previous pregnancies. The small but inevitable risks to the mother involved by Caesarean section are also, in our view, run with less justification in cases where there are already one or more children living. In all cases in which any appreciable degree of disproportion or other complication, such as an incorrectable abnormality of presentation, is present, Caesarean section is the best method of delivery, and sterilization at the time of operation should be seriously considered.

The small number of pregnancies in our series terminated by early induction makes it difficult to express an opinion on this mode of delivery in diabetics, but it has been advocated and practised with good results (Brandstrup and Okkels, 1938). The chief disadvantages of induction are its

uncertainty and the added risk of sepsis, both of which have been reduced by improved methods, of which high puncture of the membranes is particularly well suited to diabetics as, should it prove unsuccessful, no obstacle is presented to subsequent Caesarean section. Since this series was collected we have had three cases successfully delivered by this method of induction. If the technique of early induction is so improved as to exclude its present disadvantages, this would seem to be the ideal method of delivery for pregnant diabetics, but in the meanwhile Caesarean section is likely to be the most generally suitable.

Management of the Baby

Reference has already been made to the incidence of hypertrophy and hyperplasia of the islets of Langerhans in babies born of diabetic mothers, and clinical evidence of neonatal hypoglycaemia has been observed on a number of occasions, death during the first 48 hours of life having been not infrequently attributed to this cause. In order to guard against this complication we make a practice of giving all our babies two-hourly feeds of glucose in water for the first 24 hours after delivery, the interval between feeds being increased to four hours during the second day, by which time breast- or artificial feeding has been instituted and the need for glucose removed. In this way we have been able to prevent the occurrence of hypoglycaemic symptoms in all the babies of our series.

Wilder (1940) stresses the importance of the prevention and treatment of asphyxia during the early hours of life, and advocates the use of an incubator in which is maintained an oxygen concentration of 40 to 50 per cent. for the first few hours after Caesarean section; in our experience this complication has not arisen with sufficient frequency to justify these troublesome precautions.

Feeding should be attempted as early as possible and every effort made to encourage the mother to feed the baby. As has already been stated, the supply of maternal milk is often subnormal in diabetics, and test-feeding should therefore be carried out as a routine, any deficiency being corrected by supplementary feeds. Apart from the possible dangers of hypoglycaemia immediately after delivery and difficulties associated with breast-feeding, the management of the baby born of a diabetic mother differs in no way from that of any other child.

Summary and Conclusions

1. Fifty-four pregnancies in 44 diabetic women, resulting in 57 babies, are described and the findings tabulated.

2. A total foetal mortality of 33 per cent. occurred, which is a high figure. A subdivision of these pregnancies into three groups in which there was complete, partial, or no supervision of the maternal diabetes gave mortality rates of 23, 50, and 70 per cent. respectively.

3. The usual explanatory causes for this high mortality are discussed and are said to be the poor viability of the over-sized foetus, foetal hypoglycaemia, congenital foetal abnormalities, and maternal toxaemia. In our series only the first cause was noticed, and depended directly on the degree of diabetic control. We suggest that not only is over-development from hyperglycaemia present, but that many babies seem to mature three to four weeks too early, being postmature and hence poorly viable at term.

4. The main complications and difficulties are described, and the high incidence and importance of a low renal threshold in these pregnancies is stressed. This has been the cause of most of the difficulties we have met in controlling diabetic pregnant women.

5. The management of pregnancy and delivery is described. We believe that many babies are lost when pregnancy is allowed to go to full term and spontaneous delivery permitted. In the interest of the foetus, pregnancy should usually be terminated at the 36th to 38th week, and we give reasons why we are in favour of Caesarean section in primiparae and induction in multiparae.

6. We give early glucose feeds to prevent neonatal hypoglycaemia, and afterwards advise breast-feeding whenever possible.

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APPENDIX

KEY TO ABBREVIATIONS

First column

a = complete supervision
b = partial supervision
c = no supervision

w. = week
m. = months
y. = years

Insulin requirement

Ordinary type = Soluble insulin
Italic type = Protamine 'Retard' insulin
Black type = Zinc Protamine insulin
C. = Carbohydrate, in gm. per diem

Penultimate column

* Unless otherwise stated, baby was normal and survived

No. and category of case	Age at pregnancy, in years	Parity	Duration of diabetes	Daily insulin requirement (in units)						Renal threshold
				Before pregnancy	First trimester	Second trimester	Third trimester	Immediately after	Long after	
1 a	41	3	5 to 6 m. Blood-sugar 230 mg. %	0	0	0	0	0	**16** **20** (7 y. later)	Low at 5th to 6th m.
2 a	25	1	5 y.	26	30	36	80	36	30	Low at 6th m.
3 a	35	4	5 y.	0	0	18	24	12	20 (1 y.)	Low at 5th to 6th m.
4 b	22	1	?6 m., i.e. onset of pregnancy	0	0	0	34	34	34	Low at 6th to 7th m.
5 a	26	2	3rd m. of 2nd pregnancy	0	0	—	68	20	24 (3 m.)	Low at 8th m.; glycosuria +++ at 172 mg. %
6 a	32	2	<1 y.	0	0 Sugar +++ at 5th m.	76	48	30	14 (1 y.)	Low at 6th m.; glycosuria ++ at 165 mg. %
6 a	35	3	Pregnancy terminated at second m. and patient sterilized							
7 a	18	1	4 y.	80	80±	80±	80±	30	44 (1 y.)	Low at 8th m.; glycosuria ++ at 102 mg. %
7 a	19	2	5 y.	44	44±	44±	44±	30	54	Low <113 mg %
8 a	27	1	Pregnant when first seen	0	0	0	0 or 10	0	0	Low at 5th m.
8 a	30	2	3 y.	0	16	30	30	22	16	?

Ketosis	Evidence of Toxaemia: Albuminuria	Evidence of Toxaemia: Blood-pressure	Evidence of Toxaemia: Oedema	Hydramnios	Delivery	Baby*	Remarks
Short duration at 6th m.	0	120/80	0	0	Spontaneous	♂ 8 lb.	Lactosuria before and after delivery
Marked at 6th to 7th m.; cleared later on. C. 250 gm.	0	—	—	—	Caesarean section at 38th w. (spinal anaesthesia, N_2O and O_2)	♀ 9 lb. 8 oz.	Amenorrhoea cured by insulin. C. 120 to 150 gm.; raised to C. 200 to 250 gm. for ketosis
Severe at 5th m.; short duration	0	—	—	—	Spontaneous; membranes ruptured at 37th w.; labour 32 hr.	6 lb. 4 oz. Died from tentorial tear and haemorrhage into posterior fossa at 24 hr.	Required no insulin on day of delivery. Previous babies 8, 8, and 10 lb.
Severe at 5th to 6th m.; short duration	0	120/80	—	+	Spontaneous at 37th w.	5 lb. Dead 2 w.; macerated	Blood-urea, 35 mg. %. Cholesterol, 204 mg. %. C. 200 gm.
Severe at 7th m.; clear at 8th and 9th m.	0	128/70	—	Slight	Caesarean section at 37th to 38th w.	♀ 8 lb. 6 oz.	C. 180 to 200 gm. Stillborn baby 16 m. previously, weight 11½ lb.
Gerhardt's test ++ at 5th m.	0 or slight trace	120/80 to 140/90	++ (of legs)	+ at 6th m.	Spontaneous at 36th to 37th w.	♂ 6 lb. 4 oz. ♀ 6 lb. 7 oz. ? Premature twins	Blood-urea, 26 mg. %. Cholesterol, 424 mg. %. Fed both babies. First baby born same year
0	+	134/100	—	+	Caesarean section at 37th w.	♂ 8 lb. 8 oz. Almost mature	Fed baby, milk +
—	++	145/100	up to knees	Slight	Caesarean section at 37th w.	10 lb. 11 oz.	Not breast-fed. Medullary paralysis after percaine spinal anaesthesia. Mild toxaemia. B.-P. fell to 128/92. Blood-urea, 40 mg. %
Moderate	0	—	—	Acute at 24th w.	Spontaneous rupture	Abortion at 25th w.	On low carbohydrates (45 gm.)
0	0	—	—	At 24th w.	Induced at 6th m.	Dead foetus	Later sterilized. C. 120 gm. Foetal pancreas necrotic and degenerate with lymphocytic infiltration

No. and category of case	Age at pregnancy, in years	Parity	Duration of diabetes	Daily insulin requirement (in units)						Renal threshold
				Before pregnancy	First trimester	Second trimester	Third trimester	Immediately after	Long after	
9 a	21	1	3 y.	18	18	14	36	28	26	Low at 7th m.
10 a	29	1	2 y.	28	28	40	72	On 'Emergency' treatment	44	Low at 6th m.
11 b	29	2	10 m.	26	30	24	?	28 4 w. after	44 3 m. after	Not demonstrated; ?not low
12 c	—	1	Began at 4th m.	0	0	—	—	—	40	?
13 b	31	1	4 y.	0 (Had been 20, 4 y. before)	0	0	5	0	0	?
14 a	26	2	11 y.	52	52	72	128	80	92	?normal
15 c	25	1	10 y.	8	16	16	—	?	16 and 20 alternate days	?
16 a	22	1	14 y.	44	54	36 and *40*	36 and *44*	28 and *36*	22 and *42*	Low at 4th m.; 140 mg. % or less
17 a	31	1	Began at 5th to 6th m.	0	0	0	7, later 20	20	40 (1 y.)	?slightly low at 8th m.

Ketosis	Evidence of Toxaemia: Albuminuria	Evidence of Toxaemia: Blood-pressure	Evidence of Toxaemia: Oedema	Hydramnios	Delivery	Baby*	Remarks
On and off; never severe	0	115/70	Feet and ankles	—	Spontaneous at 35th w.	♂ 6 lb. 1 oz.	Admitted in labour. Breast-fed for 2 m.
Severe for 1 w. at 6th m.	+ to +++ at 8th m.	150/112 at 8th m.	++	+	Caesarean section at 38th w., and sterilization	♂ 8 lb. 13 oz.	Hyaline casts at 8th m. B.-P. fell later to 120/80. Cholesterol, 294 mg. %. Total proteins, 4·34 gm. %. Two transfusions; ultimate recovery with return of renal function to 100 %
0	No details		—	—	Spontaneous; ?4 w. premature	♂ 6 lb.	Periods always irregular, pregnancy not diagnosed until 5th to 6th m.; delivered at home
?	0	125/80	—	—	Spontaneous	Stillborn at 9th m.	—
0	0	—	—	0	Spontaneous	5½ lb.	Baby's feet swelled and circulation poor; did well; not breast-fed; mother given progynon for irregular periods
Traces	0	115/70	—	—	Caesarean section at 37th w.	7 lb. 10 oz.	First pregnancy resulted in abortion at 2nd m.; given progesterin in second pregnancy; could not feed baby long. Low diet, C. 100, P. 50, F. 65 gm.
?	+ at 33rd w.	—	—	Slight	Spontaneous at term; long labour	8 to 9 lb.; neonatal death	Blue asphyxia, and died 4 hr. after delivery
Traces; never severe	—	—	—	—	Induced about 32nd w.	Stillborn	Macerated foetus; death from torsion of cord at 31st w.
0	0	—	No details	—	Caesarean section; breech and slightly contracted pelvis; at 36th to 37th w.	8 lb. 11 oz.	Insulin stopped 2nd m. after Caesarean section; 4 m. later, insulin 5; 8 m. later, insulin 20

No. and category of case	Age at pregnancy, in years	Parity	Duration of diabetes	Daily insulin requirement (in units)						Renal threshold
				Before pregnancy	First trimester	Second trimester	Third trimester	Immediately after	Long after	
17 a	36	2	5 y.	32	—	50	98	60 to 70	34	Low at 7th m.; glycosuria + at 125 mg. %
18 a	22	2	—	56	60	70	70	40	68	Low
18 a	23	3	—	60	Same during pregnancy and after abortion				—	?
19 a	23	2	3 y.	30	28	62	40 and 72	32 and 30	36 and 20	Low from 3rd m.
20 a	28	1	7 y.	30	30 to 40	16 at 5 m.	—	26	32	? Low
21 a	24	1	2 y.	14	18	18	72	34 to 44	28	Low at 3rd m. <88 mg. %
22 a	25	1	16 m.	20 and 8	28	26	30	44 Fell to 24	44	Low at 2nd m. <94 mg. %
23 a	25	1	3 y.	48	28 and 18	36 and 60	32 and 52	24 and 40	24 and 28	Low at 5th m.
24 a	32	1	2½ y.	16	20	26	24	32	22	Low at 5th m.
24 a	33	2	4 y.	22	32	32	40	40	—	Low at 7th m.; glycosuria ++ at 157 mg. %
25 a	29	1	4 y.	38	42	60	60	66	42 12 days later	Low at 5th m.

Ketosis	Evidence of Toxaemia: Albuminuria	Evidence of Toxaemia: Blood-pressure	Evidence of Toxaemia: Oedema	Hydramnios	Delivery	Baby*	Remarks
Severe at 26th w.; short duration	0 or slight trace	115/75	+	+ at 33rd w., less at 36th w.	Caesarean section at 36th to 37th w.	10 lb. 4 oz.	Breast-fed entirely
0	0	—	0	—	Indueed at 40th w.	9 lb. 12 oz.	—
Trace to moderately severe from 1st to 3rd m.	—	—	—	—	Aborted at 3rd to 4th m.	—	Sterilized; another child not wanted
Severe at 31st to 32nd w.; eleared and no return	0	120/78	+ (last 2 m.)	+	Caesarean section at 36th to 37th w.	♀ 9 lb. 12 oz.	Breast-fed. Stillborn child 2 y. before, indueed at 8th m.
Never marked	0	—	—	++	Caesarean section at 26th w.	26-week foetus; did not survive	C. 130 gm. Had continuous evipan anaesthesia; therapeutic abortion
Severe at 7th m.	+	105/75	+ (legs)	+	Caesarean section at 37th w.	♀ 9 lb. 9 oz.	C. 220 gm.
Not marked	0	124/74	—	—	Spontaneous at ?8th m.	♂ 7 lb. 2 oz.	Fed baby for short while
+ at 2nd m. + at 5th m. ++ at 7th m.	0	120/80	0	—	Caesarean section at 38th w.	♀ 11 lb. 11½ oz.	Finger-nails full length; toe-nails short; mother given blood transfusion
Never marked	0	120/80	0	—	Caesarean section at 38th w.	11 lb.; died at about 24 hr.	Caesarean section postponed on account of scabies; baby's finger-nails full length; toe-nails short
Never marked	0	106/60	0	+	Caesarean section at 37th to 38th w.	♂ 8 lb. 14 oz.	Baby's blood-sugar (from cord) 105 mg. %
Began at 4th m.; +++ at 5th m.; cleared later	0		No details		Caesarean section at 40th to 41st w.	8 lb.; stillborn foetus	Foetus died at ?39th w.; diabetes immediately worse; mother died, pulmonary embolus, 12 days after operation. C. 75 gm.

No. and category of case	Age at pregnancy, in years	Parity	Duration of diabetes	Daily insulin requirement (in units)						Renal threshold
				Before pregnancy	First trimester	Second trimester	Third trimester	Immediately after	Long after	
26 a	29	1	2 y.	20	26 C. 40 gm.	36 C. 75 gm.	26 at 33 w.; 0 at 36 w.; 18 at 37 w.; C. 80 to 140 gm. for last 2 w.	40	40 to 50; now 35	Low at 4th m.
27 c	26	1	2¼ y.	—	—	—	—	—	—	?Low always
27 c	28	2	5 y.	—	—	—	—	—	—	—
28 c	24	1	3 y.	—	—	—	—	—	—	—
28 c	26	2	5 y.	Always about 20				—	—	—
28 c	28	3	7 y.	—	—	—	—	—	—	—
29 a	24	3	14 y.	40 and 8	40 and 8 and 8	26 and 26 and 12	28 and 28 and 18	24 and 24	—	Low at 6th m.
30 a	28	1	4 y.	60	60	70	72	48	—	Low at 7th m.
31 b	33	1	Discovered at 2 m.	0	18	24 and 8, later 36 and 24 and 16	36 and 24 and 16	32 and 16, later 32	14 and 12	Low at 2nd m.
32 a	29	1	2 y.	36	32 and 8	32 and 12 and 8	—	28 and 8	28 and 12	No evidence that it was low, ?normal
33 a	23	2	10 y.	12	12	12	12, later 14 and 16 for 1 w.	14 and 16 for 2 w.	0 sugar +++ at 4 m.	?

Ketosis	Evidence of Toxaemia: Albuminuria	Evidence of Toxaemia: Blood-pressure	Evidence of Toxaemia: Oedema	Hydramnios	Delivery	Baby*	Remarks
+ during all pregnancy until last 2 w.	++ (granular casts ++, hyaline casts ++; both absent after delivery)	—	++	+	Caesarean section at 39th w.	4 lb. 10 oz. 8 lb. 6 oz. (dizygous twins)	Enormous oedema; diuretics in last 6 w. Mother's weight before labour = 12½ st., 2 w. after = 8¼ st. Cholesterol, 150 mg. %. Blood-urea, 25 and 42 mg. %. Maternal blood-sugar, 150 mg. %. Foetal blood-sugars, 86 mg. and 68 mg. %
Not marked	—	—	—	—	Spontaneous	Twins, stillborn at 30th to 31st w.	Mother had diabetic cataracts
—	—	—	—	—	Spontaneous	Stillborn at 7th m.	Not seen during pregnancy
—	—	—	—	—	Spontaneous	9 lb.	Never attended King's College
—	—	No details		—	Spontaneous	♀ 11 lb.	Hospital for pregnancies or even
—	—	—	—	—	Spontaneous	♀ 11 lb.	saw doctor for second and third pregnancies. C. 100 gm.
+++ at 8th m.; cleared later; never prolonged	0	120/70	—	0	Caesarean section at 38th w.	♀ 7 lb.	Much hypoglycaemia during pregnancy. First pregnancy, premature birth at 7th m.; lived 1½ hr.; weight 4½ lb.; second pregnancy aborted at 3rd m.
Not marked	0	120/80	—	0	Caesarean section at 37th w.	♂ 8 lb. 4 oz.	—
Severe from 3rd to 5th m.; then slight	0	120/80	—	—	Caesarean section done during labour at 35th w.	♂ 7 lb. 2 oz. Died after 10 hr., of atelectasis	Admitted in labour with membranes ruptured
Not marked	Slight, later ++	140/100 at 34th w., later 160/110	+	+	Caesarean section at 36th to 37th w.	♂ 7 lb. 12 oz. ? Congenital heart disease	Admitted with toxaemia at 34th w.
?	+ later trace	120/80; had been 134/84	+ later 0	Slight	Spontaneous; induced at 37th w.	♀ 8 lb. 2 oz.	Little milk only; first baby stillborn

No. and category of case	Age at pregnancy, in years	Parity	Duration of diabetes	Daily insulin requirement (in units)						Renal threshold
				Before pregnancy	First trimester	Second trimester	Third trimester	Immediately after	Long after	
34 c	26	3	During pregnancy	0	0	0	0 C. 150 to 200 gm.	0	0	—
34 a	28	4	2 y.	0	0 Blood-sugar curve nearly normal	0	0	0	0	Low at 8th m.
35 a	39	1	2 y.	30	—	—	60	30 (caused hypoglycaemia)	32 and 10	No clear evidence, ? not low
36 a	39	2	19 y.	40 C. 80 gm.	—	—	74 C. 190 gm.	44 at 2 w. = 18; at 3 w. 0 for 3 days; at 4 w. = 10; at 8 w. = 16	38	Very low < 96 mg. %
37 c	24	2	10 y.	8 once a w.	—	8 almost daily			—	?
38 a	31	1	8 y.	38	38	38	68	42	40	Low < 140 mg. %
39 a	28	1	10 y.	30	—	—	74	34	34	Low < 114 mg. %

Ketosis	Evidence of Toxaemia: Albuminuria	Evidence of Toxaemia: Blood-pressure	Evidence of Toxaemia: Oedema	Hydramnios	Delivery	Baby*	Remarks
—	—	—	—	—	Spontaneous	9 lb. Macerated foetus	First seen at 9th m.; admitted to hospital in labour
++ at 8th m. 0 at 9th m.	0	—	++	—	Premature; spontaneous	Stillborn; foetal death at 8½ m.	Almost normal blood-sugar curve at 8th m.; low threshold and ketosis +++ during curve. First pregnancy, abortion at 4th m.; second pregnancy, stillbirth at term
0	0	135/85	++	+	Caesarean section at 37th w.	♂ 7 lb. 4 oz. Mature	Severe anaemia; red cells 2,300,000; Hb. 40 %. Artificial feeding. Not seen until 8th m.
+++ when first seen, absent later	0	110/70	0	+	Caesarean section at 37th w.	♀ 7 lb. 11 oz.	First seen at 30th w.; little milk only. First baby 9 y. proviously; no details known
0	0	120/80 to 130/80	—	—	Caesarean section at 37th w.	♀ Average size. Died 24 hr. after birth with blue asphyxia; oedema of brain; no haemorrhage	Sugar ++++ always. Post mortem showed oedema of brain, but no haemorrhages. First baby, spontaneous delivery at term; died 4 hr. later in blue asphyxia. Post mortem nil abnormal
+++ at 5th m., absent later	0	140/80 to 150/90	0	0	Caesarean section at 37th w.	♂ 9 lb. 8 oz.	Breast-fed. Blood-sugar at birth. Maternal, 308 mg. %. Umbilical vein, 248 mg. %. Umbilical artery, 157 mg. %
At 5th m.	0	114/74	0	0	Caesarean section at 37th w.	5 lb. 8 oz. Died in 3 hr.	—

No. and category of case	Age at pregnancy, in years	Parity	Duration of diabetes	Daily insulin requirement (in units)						Renal threshold
				Before pregnancy	First trimester	Second trimester	Third trimester	Immediately after	Long after	
40 c	40	11	?8 y.	15	15	45 C. 69 gm.	66 C. 150 gm., later 200 gm.	0	0 for 15 m., later 188	Low at 6th m. 130 mg. %
41 a	30	1	1¾ y.	20 and 16	12 and 12	12 and 16	16 and 20	6 and 16	—	At 5th m. low, trace at 100 mg. % At 6th m. +++ at 148 mg. %
42 a	31	3	4 y.	56	48	48	56 to 64	40	—	?
43 a	33	1	6 y.	32 and 24	28 and 24	36 and 36	40 and 40	32 on 1st day 32 and 20 on 4th day	36 and 24, 5 w. after	Low at 5th m., glycosuria +++ at 150 mg. %
44 a	24	1	14 y.	40 and 4	40 and 4 to 8	40 and 16 and 6 to 12	48 and 44	—	—	Low at 3rd to 4th m., ++ at 149 mg. %

Ketosis	Evidence of Toxaemia: Albuminuria	Evidence of Toxaemia: Blood-pressure	Evidence of Toxaemia: Oedema	Hydramnios	Delivery	Baby*	Remarks
+++ at 8th and 9th m.	0	—	+	++	Spontaneous (forceps)	12 lb. 6 oz. Stillborn; tentorial tear and cerebral haemorrhage during delivery	Onset at 32 y. Aged 25 to 32, had six babies of between 7 and 9 lb., five of whom lived. Aged 32 to 39, had one abortion and three stillborn babies of between 12 and 15 lb.
0	Trace	130/80 at 3rd m.; 150/98 at 8th m.; 140/107 at 9th m.	++	+	Spontaneous at 38th to 39th w.	♀ 8 lb. 8 oz.	Toxaemia of pregnancy. Urea clearance = 51 % of normal (1 w. before delivery). C. 200 gm.
0	Very slight trace	120/85	?	+	Caesarean section at 36th w.	♀ 6 lb. 5 oz.	Mother anaemic. Baby's finger-nails full length; toe-nails slightly short
Severe at 5th m. for 1 w.; severe at 7th m. for 1 to 2 w., but not after	Trace at 5th m.	110/75 at 20th w.; 100/60 at 36th w.	Slight (of ankles)	+	Caesarean section at 37th w.	♀ 8 lb. 13 oz.	Mother, renal calculus and urinary infection; pigmentation of face; anaemic with Hb. 78 % before and 36 % after operation; transfused twice; recovered
Severe at 7th m. for 2 w., but cleared later	0	120/70	—	++	Caesarean section during labour	♀ 8 lb. 5 oz.	Caesarean section because poor progress in labour

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CRITICAL REVIEW

AZOTAEMIA IN GASTRO-DUODENAL HAEMORRHAGE[1]

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Introduction

In 1914 Tileston and Comfort discovered, in an investigation on intestinal obstruction, that the amount of urea in the blood might be substantially increased in the absence of demonstrable disease of the kidneys. Richard Bright had known that the blood-urea was raised in nephritis, but the discovery that the blood-urea might be increased in the absence of renal disease prompted a search for 'extrarenal uraemia', similar to that found in intestinal obstruction, in other conditions. It was soon found that such a rise in blood-urea was not uncommon, being liable to occur in diarrhoea and vomiting from any cause, Addison's disease, fevers, acute yellow atrophy of the liver, diabetic coma, and many other diseases. In patients with severe bleeding into the stomach or duodenum from whatever cause, the blood-urea is almost always increased, in many cases to values of 100 mg. per 100 c.c. and upwards. Although this type of azotaemia was not recognized until 1933, the frequency with which it occurs has made it a favoured subject of study, and an extensive literature has accumulated in the past few years. Many of the published papers have been concerned with observations on a considerable number of patients, but while this method of investigation has served to demonstrate the constancy of a rise in blood-urea after haematemesis, and to define the time of onset, height, and duration of the azotaemia, it has failed to explain the source of the increased amount of urea in the blood and the factors which prevent its prompt elimination by the kidneys, problems whose solution is essential to an understanding of the causes of this type of azotaemia. More recently, intensive laboratory studies have been carried out on small numbers of typical patients in order to obtain more detailed information than could accrue from the limited range of investigations which can be carried out on a large series; also, attempts have been made to duplicate the condition experimentally, both in animals and man, a method which enables the relative importance of individual actiological factors to be assessed more readily than does observation of patients in whom various potential causes are acting together. The amount of knowledge which has been gained in these various ways makes possible a fairly accurate picture of the natural history and the causes of this type of azotaemia.

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General Features of the Azotaemia

Course of the azotaemia. The frequency with which an elevation of blood-urea occurs after haematemesis may be gauged from the figures in Table I, based on the maximum value for blood-urea in 24 patients reported by Witts (1937), 53 patients of Schiff and Stevens (1939), in addition to 56 patients observed by me. Thirty-one of the 133 patients show no elevation of blood-urea above the upper normal limit of 50 mg. per 100 c.c., while the majority of the patients show a moderate elevation, with blood-urea between

TABLE I

Frequency and Degree of Azotaemia in 133 Patients with Haematemesis

Blood-urea per 100 c.c.	Number of patients in each group	Percentage of series in each group
Less than 50 mg.	31	23
Between 50 and 100 mg.	69	52
More than 100 mg.	33	25
Total	133	

50 and 100 mg. per 100 c.c. These figures are derived from patients in whom the bleeding had been severe enough to cause admission to hospital; if mild cases of bleeding from peptic ulcer were included, the incidence of azotaemia would be much lower. The rise in blood-urea may be present very soon after the haemorrhage, and we have observed a figure of 83 mg. per 100 c.c. within two hours of the onset of symptoms of bleeding; Bookless (1938) and Schiff and Stevens (1939) have recorded similar figures at two and five hours respectively. It is possible, of course, that in these cases there may have been some bleeding before symptoms were manifest, but Hesser (1933), studying the duration of bleeding in the patient with peptic ulcer, believed that the pulse-rate, skin-colour, blood-pressure, and general clinical condition were good guides in determining whether bleeding was present. Meulengracht (1935) expressed the opinion that the actual bleeding could last only a short time; it must therefore be quite rapid, and the onset of symptoms both from blood loss and from gastro-duodenal distension will also be rapid, and so will serve reasonably well to mark the onset of haemorrhage. In general, the blood-urea is at its height on the day after haemorrhage, but falls rapidly to a level of about 50 mg. per 100 c.c., at which height the azotaemia persists for a week or longer before completely normal blood-urea values are obtained. When the haemorrhage is very severe, the blood-urea may continue to rise for some days, and in fatal cases a continuous increase in blood-urea takes place. In patients with recurrent haemorrhage the onset of fresh bleeding is attended by a secondary rise in blood-urea, similar to that observed at the time of the initial bleeding, but often surpassing it in degree. The rate of subsidence of the azotaemia can be notably increased by slow drip blood transfusion (Wood, 1936), but not by the infusion of plasma in comparable amount (Black and Smith, 1941).

Since the azotaemia of haematemesis occurs at a time when the patients are suffering from severe blood loss and from a restricted intake of fluid, it is hard to decide to what extent the azotaemia itself is responsible for the picture of acute illness which they present. Headache and thirst are the outstanding complaints on admission to hospital, and although the patients are commonly restless, convulsions or muscular twitchings of the type seen in nephritic uraemia do not occur. When one considers that the haemoglobin may fall to half its previous level in a few hours, it is surprising that respiratory distress is not more prominent; air-hunger is not noticeable, and a respiratory tracing shows no increase either in the rate or depth of breathing. The clinical picture resembles in some ways that of traumatic shock, since pallor, asthenia, collapsed veins, and a thin rapid pulse are common to the two conditions, but the shock syndrome is not so dominant or so persistent after haematemesis as after bleeding from lacerated wounds. Jones (1939 *b*) has made important observations on the blood-pressure after haematemesis. After a small haemorrhage the blood-pressure was usually within normal limits, or even slightly raised—the phase of reactive hypertension which may also be seen in patients with surgical shock. With more severe bleeding a fall in systolic pressure to 90 mm. or less occurred, although this fall in blood-pressure was usually transient, the blood-pressure beginning to rise in an hour or so, even in patients who were not transfused. There is no direct correlation between the blood-urea level and either the pulse-rate or the systolic blood-pressure. As might be expected, those patients who have been admitted after recurrent haemorrhage show signs of severe dehydration, with coated tongue and wrinkled skin. Considerable loss of weight may occur after gastro-duodenal haemorrhage (Bookless, 1938). Black and Leese (1940) have observed that this weight loss takes place even when the fluid intake is adequate, so that there is probably actual wasting of the tissues, as well as loss of fluid.

Factors influencing the azotaemia. The character of the lesion underlying gastro-duodenal haemorrhage seems to be without influence on the degree of azotaemia, except in so far as the nature of the lesion conditions the severity of the haemorrhage. It would therefore be out of place to discuss in any detail the various possible causes of haematemesis, of which Hurst (1929) gives a full account. It may be said that severe azotaemia is most common in bleeding from simple gastric or duodenal ulcer, including multiple gastric erosions (Jennings, 1936), while carcinoma of the stomach and gastric varices secondary to portal cirrhosis are less common causes. The age of the patient does not appear to influence the height of the azotaemia, but pre-existing renal disease increases and prolongs the rise in blood-urea. Christiansen (1937) has stated that 'in "simple" haematemesis, where the greater part of the blood is vomited while only a small part passes on into the intestinal canal, there appears no rise in the blood-urea concentration'. It is very uncommon for patients to have a haematemesis without melaena developing in the next few days, and our impression is contrary to that of Christiansen,

in that patients with severe vomiting have had a greater rise of blood-urea than those in whom vomiting was slight or absent. A raised blood-urea can occur even when adequate amounts of food and fluid are administered, but Jones (1939 *a*) has shown that dehydration is always present in patients with exceptionally high blood-urea values. It might be expected that the rapidity of the haemorrhage might have an influence on the blood-urea increase, but the values for blood-urea are not noticeably higher in those patients in whom severe signs and symptoms of shock bear witness to a sudden and rapid haemorrhage.

Results of Special Investigations

Blood count. It is well known that for the first few hours after bleeding from peptic ulcer the haemoglobin percentage is quite unreliable as a guide to the severity of the haemorrhage (Bennett, Dow, Lander, and Wright, 1938). The physiological response to haemorrhage is a dilution of the blood by the entry of fluid from the tissues, but the rapidity with which haemodilution takes place is affected by the rate of the haemorrhage, the amount of fluid available in the tissues, and the presence of shock (Robertson, 1938). The time at which blood dilution is greatest varies, but generally lies between six and forty-eight hours after the apparent onset of the haemorrhage. If repeated estimations of haemoglobin are made, the lowest value observed gives an indication of the amount of blood lost; in a patient with severe haematemesis the lowest haemoglobin percentage is 40 per cent. or less, so that more than half of the original amount of circulating red cells must have been lost. The red-cell count and haematocrit percentage are diminished in proportion to the fall in haemoglobin. The red cells are at first normal in size and haemoglobin content, but when the bleeding is severe or recurrent small hypochromic erythrocytes appear, as in other types of post-haemorrhagic anaemia. A leucocyte count of 20,000 per c.mm. or more is usual for a day or two after the bleeding. There is no close relation between the degree of anaemia and the blood-urea level (Alsted, 1936 *a b*), although in general patients with very severe anaemia tend to have a high blood-urea (Schiff and Stevens, 1939).

Blood-volume. After any severe haematemesis the blood-volume is reduced; at first the red-cell volume and plasma-volume are diminished equally, but during a period which varies from a few hours to several days the plasma-volume is made up to normal by the entry of fluid from the tissues, whereas the red-cell volume remains low until blood regeneration is complete. In the majority of patients some hours have elapsed before the blood-volume is determined, and the red-cell volume is usually found to be low, while plasma-volume is normal and total blood-volume is reduced only because of the low red-cell volume. The reduction in red-cell volume is a large one; in a series of 122 patients Bennett, Dow, Lander, and Wright (1938) found no less than 57 whose total red-cell volume was diminished by more than 50 per cent. In some patients with a very low red-cell volume,

the plasma-volume may be increased above normal, but there seem to be physiological limits to this process of haemodilution beyond which the concentration of haemoglobin is maintained even at the expense of a low blood-volume. During recovery the red-cell volume rises slowly to normal, as new red cells are formed to replace those lost by bleeding; on the other hand, recurrence of haemorrhage is attended by a further fall in red-cell volume. While low blood-volume and severe azotaemia are often found together, the presence of a low blood-volume is not essential to the production of azotaemia. We have observed blood-urea values of more than 70 mg. per 100 c.c. in eight patients whose total blood-volume was 4·5 litres or more. An analysis of the figures obtained in 28 patients with haematemesis, in whom blood-urea and red-cell volume were determined at the same time, showed that there was little correlation between the two values. The blood-urea averaged 80 mg. per 100 c.c., with a standard deviation of ± 39; the average total volume of circulating red cells was 1·09 litres, with a standard deviation of $\pm 0{\cdot}45$. The coefficient of correlation between blood-urea and total red-cell volume was $-0{\cdot}23$; since the standard error of a series of 28 terms is 0·19, the negative correlation observed might be attributed to sampling error, and cannot be regarded as close.

Biochemical estimations on blood. The character and duration of the changes in blood-urea have already received comment. The increase in urea-nitrogen accounts for the greater part of the azotaemia, but there is also a slight increase in residual nitrogen, that is, non-protein nitrogen minus urea-nitrogen. Ingegno (1935) found no increase in creatinine or in uric acid nitrogen, but Black (1941) has found a moderate rise in amino-acid nitrogen, the usual figures being from 10 to 20 mg. per 100 c.c. as compared with the normal values of 5 to 8 mg. per 100 c.c. The plasma protein nitrogen does not contribute to the azotaemia, for plasma protein is usually diminished, the albumin to a greater extent than the globulin (Borst, 1936 *a*). Plasma-chloride was found to be raised in eight out of nine patients by Borst (1936 *a b*, 1938); and Allott (1939) and Black and Leese (1940) have each studied one patient in whom the plasma-chloride was raised after a severe haematemesis. No other worker has found the plasma-chloride raised so frequently as Borst claims it to be, and it is the general experience that at the time when the blood-urea is rising there is no alteration in plasma-chloride (Ingegno, 1935; Christiansen, 1937; Witts, 1937; Azzolini and Carboncini, 1938; Schiff and Stevens, 1939; Johnson, 1941). Black and Leese (1940) found that the plasma-chloride fell below normal in the days following haemorrhage, and a similar fall in total plasma-base was observed. Plasma bicarbonate is normal, unless vomiting is so severe as to cause alkalosis. The serum-calcium is within normal limits (Bick and Wood, 1941).

Urine findings. For the first 24 or 48 hours after alimentary haemorrhage, the urine volume is low, usually less than 1 litre per diem. Later, when the azotaemia is subsiding, the urine volume increases, and Jones (1939 *a*) described actual diuresis in association with the increased output of urea at

this time. The specific gravity of the urine is not diminished, the average value in 17 of our patients being 1·023. The reaction of the urine is usually acid. Frank albuminuria was present in two of our 17 patients, and three others had traces of albumin; Bookless (1938) found albumin in five of 13 patients, and Azzolini and Carboncini (1939) in two of nine patients. None of the 17 urines which we examined contained red blood-cells; hyaline or granular casts were present in small numbers in three urines. The concentration of urea in the urine is good, and commonly exceeds 3 gm. per 100 c.c.; the daily excretion of urea is not diminished below that found in normal patients (Meyler, 1935 *a b*). On the other hand, the urinary output of chloride is very low indeed, and total base excretion is also reduced, although Borst (1938) found the potassium output higher than normal. The nitrogen partition in the urine is within normal limits, though the proportion of urea nitrogen is higher than usual; creatinine, uric acid, and ammonia excretion are normal. We have observed creatinuria in one patient, and bilirubinuria is another occasional finding (Clausen, 1935).

Renal function tests. Although patients with haematemesis quite often excrete as much urea in the 24 hours as a normal person, it cannot be assumed from this that kidney function is normal in these patients, for Addis (1922, 1928) has shown that the output of urea is of value as a measure of renal function only when it is considered in relation to the blood-urea level. A test such as the urea clearance test of Van Slyke, which determines the amount of blood which would be totally cleared of urea each minute, may therefore reveal a defective renal function even when the output of urea in the urine is quite high. Depression of the urea clearance has been observed in the majority of patients with post-haemorrhagic azotaemia who have been studied in this way (Alsted, 1936 *a*; Black, 1939; Johnson, 1941). There is not, however, any very close relation between urea clearance and blood-urea level, although in general the blood-urea is higher in those patients in whom urea clearance is most depressed. The fall in urea clearance is also unrelated to fall in blood-pressure or haemoglobin percentage, but is more closely associated with a diminished total red-cell volume (Black, 1939).

In order to obtain more detailed information about renal function than is afforded by the urea clearance test alone, several workers have carried out clearance tests with inulin, phenol red, and organic iodine as devised by Smith (1939). In general terms it may be stated that inulin clearance measures the amount of glomerular filtrate, phenol red clearance varies with tubular activity, and the effective renal plasma flow may be measured by the clearance of diodone (B.P.), an organic iodine compound which is used in pyelography as Diodrast, Perabrodil, or Pyelodil. Stevens, Schiff, Lublin, and Garber (1940) found that after haematemesis the clearance of inulin and of phenol red was reduced in some patients, but not in others. Unfortunately, it cannot be determined from their figures whether the azotaemia was waxing or waning at the time when their observations were made, and this is a point of importance, because Black, Powell, and Smith (1941) found that, when

the blood-urea was rising, the inulin clearance might be reduced to less than half of the value obtained after recovery, but when the azotaemia was subsiding inulin clearance was normal or even increased. Diodone clearance was found to be diminished at the same time as inulin clearance, and to an even greater extent. The reduction in the clearance of inulin and diodone bore no close relation to fall in blood-pressure or blood-volume; when a low blood-volume was raised to normal by transfusion, diodone and inulin clearance improved, but did not attain normal values until the patient had fully recovered.

Metabolic observations. In patients with gastro-duodenal bleeding there is no general increase in metabolism, as estimated by the basal metabolic rate

TABLE II

Nitrogen Absorption from Blood in the Bowel

Case	Iron in faeces in gm.	Calculated nitrogen in shed blood in gm.	Nitrogen in faeces in gm.	Nitrogen absorbed in gm.
1	1·05	75	30	45
2	0·30	27	4	23
3	1·86	144	10	134

(Black, 1940 *a*). Metabolic balance experiments in these patients are difficult to interpret, because the blood effused into the bowel represents a source of nitrogen and other substances, yet it is not possible to determine exactly either the quantity or the nitrogen content of the effused blood. Black and Leese (1940) have attempted to surmount this difficulty by assuming firstly, that the amount of iron absorbed or excreted by the bowel is negligible in comparison with the iron content of the effused blood, so that the iron content of the faeces over a period will correspond approximately to the iron content of the shed blood, and secondly, that the iron : nitrogen ratio of the blood effused into the bowel is similar to that of the circulating blood. If these assumptions are valid, it is possible, using the iron content of the faeces and the iron : nitrogen ratio of the circulating blood at the time of haemorrhage, to calculate the amount of nitrogen which should be present in the faeces provided that no absorption of nitrogen had taken place; the difference between this calculated amount of nitrogen and the observed nitrogen content of the faeces gives the amount of nitrogen absorbed from blood in the bowel. The values obtained in three patients are shown in Table II. It is evident from these figures that the greater part of the nitrogen in the effused blood was absorbed. When the intake of nitrogen from the blood in the bowel was included, the patients were in positive nitrogen balance, although the daily output of urea was normal or even high. The observed retention of nitrogen was large, amounting on the average to 5 gm. per diem during the period of azotaemia. In spite of the positive nitrogen balance, patients with haematemesis lose weight, and Black and Leese (1940) found increased excretion of inorganic sulphur and

phosphorus, consistent with an increase in the breakdown of tissue protein (Landauer, 1894). The chloride balance, like that of nitrogen, was positive. The amount of chloride in the urine was very small, and although the greater part of the chloride in the effused blood was absorbed, small amounts of chloride were present in the faeces.

Experimental Evidence

The information derived from observation of patients with haematemesis has been supplemented by experimental work in man and animals on the effects of haemorrhage and of giving blood by mouth, and by observations on patients with anaemia, shock, and vomiting from causes other than gastro-duodenal haemorrhage.

The blood-urea after haemorrhage. After a severe gastro-duodenal haemorrhage the haemoglobin percentage falls from the normal figure of 100 or more, to 30 or 40 per cent., indicating that more than half the blood-volume has been lost. It is not possible to deprive donors of two litres of blood, which would be of the same order as the blood loss in haematemesis, but the effect of withdrawing smaller amounts of blood has been studied in a series of 27 volunteers by Wallace and Sharpey-Schafer (1941). Blood-withdrawal was stopped whenever any fall in blood-pressure appeared; even so, 13 of the patients lost amounts of blood from 1,000 to 1,150 c.c. After haemorrhage of this order, the time taken for blood dilution to be complete was very variable, from 3 to 90 hours. Although fall in blood-pressure occurred in all the patients, and many of them became unconscious, there was no rise in the blood-urea except in three patients with pre-existing renal damage. Although haemorrhage as severe as may occur in gastro-duodenal bleeding has not been deliberately produced in man, a slight increase in the non-protein nitrogen has been observed by Duval and Grigaut (1918) in patients with wound haemorrhage. Here, too, the haemorrhage is complicated, not by the presence of blood in the bowel, but by the occurrence of surgical shock, so that the only possible way of studying uncomplicated haemorrhage of the order of severity which may be met with in severe haematemesis is in experimental animals. After removal of an amount of blood equal to half the calculated blood-volume, a rise in blood-urea or non-protein nitrogen of about 15 mg. per 100 c.c. has been observed in animals by Taylor and Lewis (1915), Vallery-Radot, Mauric, Hugo, and Gauthier-Villars (1935), Kaump and Parsons (1940), and Black (1940 *b*). This very mild azotaemia is not modified by combining haemorrhage with the injection of cortin or adrenalin. Meyler (1935 *b*) found that repeated haemorrhage combined with fluid deprivation would produce a much greater rise in blood-urea, to 200 mg. per 100 c.c. In addition to the rise in blood-urea an increased excretion of nitrogen is observed after haemorrhage (Buell, 1919; Stewart and Rourke, 1936).

The blood-urea after oral administration of blood. Amounts of blood up to two litres have been fed to man by Sanguinetti (1934), Sučić (1935), Meyler

(1936), and Clausen (1936), and all these workers found a rise in blood-urea, except Sučić who gave the blood in divided doses and did not estimate the blood-urea until 24 hours after the blood was given. A rise in blood-urea after feeding blood has also been reported in rabbits by Junet and Sciclounoff (1939) and in dogs by Kaump and Parsons (1940), Yuile and Hawkins (1941), and Chunn and Harkins (1941). Schiff, Stevens, Goodman, Garber, and Lublin (1939) have carried out the most complete experiments on blood feeding, using 15 patients without obvious renal disease. They found that a rise of blood-urea followed the giving of as little as 250 c.c. of blood, and that when 2 litres of blood were given over an eight-hour period the blood-urea curve was somewhat similar to that observed after haematemesis. The peak of blood-urea was not reached until 8 or 12 hours after giving the blood, and at four hours the blood-urea was never higher than 70 mg. per 100 c.c. The rise in blood-urea was roughly proportional to the amount of blood given, and the blood appeared to act merely as a source of nitrogen, since the same type of blood-urea rise could be obtained by giving the same amount of protein in the form of meat. The increase in blood-urea was not brought about by impaired renal function, for inulin clearance tests were normal after blood feeding.

The blood-urea in anaemia, shock, and vomiting. Patients with severe chronic anaemia sometimes show an elevation of the blood-urea to 50 or 60 mg. per 100 c.c., while leukaemic patients have an even greater increase. This degree of elevation of the blood-urea is not comparable to the azotaemia of haematemesis, and we have already seen that in that condition the height of the azotaemia bears little relation to the degree of anaemia. Patients suffering from shock have as a rule a normal blood-urea for some hours (Black, 1940 *c*), although a day or two after injury patients may have a raised non-protein nitrogen because of depressed renal or hepatic function. Severe vomiting is well known to be associated with a pronounced rise in the blood-urea, caused not only by loss of fluid, but by the presence of alkalosis which impairs renal function (Cooke, 1932). In patients with gastro-duodenal bleeding the plasma bicarbonate is normal; it is therefore unlikely that vomiting is an important cause of azotaemia in these patients, and indeed severe or prolonged vomiting is uncommon unless pyloric stenosis is present as a complication.

Causes of the Azotaemia

A list of the explanations which have been put forward for the azotaemia of gastro-duodenal haemorrhage is given in Table III. Since it is not possible to correlate the height of blood-urea closely with any one factor, such as blood-pressure, blood-volume, urea clearance, or haemoglobin percentage, we must suppose not only that more than one of these suggested mechanisms may be operative in any given patient, but that different patients may owe their azotaemia to different groups of factors. A close analysis of these factors need not be a vain or useless task, for an apparently complex

network of proximate causes may be found on examination to depend on one or two ultimate causes which are susceptible to therapy.

We have seen in our description of the general features of the azotaemia that the majority of patients show only a moderate rise of blood-urea, but that some may develop a more pronounced azotaemia; it is clear that any

TABLE III

Suggested Causes of Azotaemia after Gastro-Duodenal Haemorrhage

A. *Increased formation of non-protein nitrogen*

(1) Blood in the bowel, acting as
  (*a*) a source of nitrogen (Sanguinetti, 1934; Serre, 1938; Schiff, Stevens, Goodman, Garber, and Lublin, 1939);
  (*b*) a cause of toxaemia (Christiansen, 1937).
(2) Increased breakdown of tissue protein, caused by
  (*a*) dehydration (Meyler, 1935 *b*; Jones, 1939 *a*);
  (*b*) 'demineralization' (Christiansen, 1937; Sučić, 1935);
  (*c*) shock and diminished blood-volume (Bookless, 1938).
(3) Liver damage (Azzolini and Carboncini, 1938; Kobro, 1938; Polack, 1936).

B. *Diminished elimination of non-protein nitrogen*

(1) Functional renal impairment, caused by
  (*a*) low blood-pressure (Alsted, 1936 *a*);
  (*b*) deficient blood supply to kidney tissue (Wood, 1936);
  (*c*) toxic effect on kidney (Christiansen, 1937);
  (*d*) salt and water deficiency (Sučić, 1935).
(2) A previously latent renal lesion (Cain, Cattan, and Zarachovitch, 1938; Warembourg and Démarez, 1938).

explanation of the azotaemia must account not only for the usual moderate elevation, but also for the occasional rise of blood-urea to 200 mg. per 100 c.c. or more. To be complete it must define the source of the urea which is present in excess of the normal amount, and must also account for the failure of the kidneys to excrete this excess. Such an explanation can come only from a detailed examination of the factors which are at work to disturb protein metabolism and impair the renal excretion of urea. It is theoretically possible that rise in urea concentration might occur without actual increase in the total quantity of urea in the body, owing to diminution in the volume of fluid over which the urea is distributed. Since urea is freely and rapidly diffusible, the whole volume of body water, both intra- and extra-cellular, must be considered. Even in severe dehydration the loss of fluid is only about six per cent. of the body weight, or 10 per cent. of the body fluid (Maddock and Coller, 1937), so that mere diminution of body fluid is not competent in itself to produce a rise in blood-urea of more than 5 mg. per 100 c.c. There must, therefore, be an absolute increase in the urea content of the body, and it is possible to arrive at a fairly accurate estimate of the size of this increment. If the urea content of the fluids were increased by 50 mg. (0·05 gm.) per 100 c.c., the amount of excess urea in 50 litres of body water would be 25 gm., corresponding to 12 gm. of urea nitrogen, and capable of being produced by the katabolism of 80 gm. of protein. In other

words, the amount of excess non-protein nitrogen in the body when the blood-urea is raised by 50 mg. per 100 c.c. is roughly equivalent to a normal daily protein intake or urea excretion. Increase in the urea content of the body must be referable either to an increased rate of formation, or a diminished rate of elimination of urea, or to a combination of these processes. We must now consider in what respects urea formation and elimination may be modified in patients with gastro-duodenal bleeding.

Formation of urea. It is well recognized that the first stage in the katabolism both of food and tissue proteins is the separation of the protein into its constituent amino-acids (Folin, 1905). These may then be utilized once more in protein formation, or they may be converted into urea. In gastro-duodenal haemorrhage there are three possible sources of nitrogenous end-products, the protein of the tissues, of the food, and of the blood shed into the bowel. The food protein may be left out of account as the cause of increased urea formation, since it is itself diminished rather than increased in amount; the blood in the bowel and the protein of the tissues remain as the possible sources of non-protein nitrogen.

Blood in the bowel. Attention was first directed to the presence of blood in the bowel as a possible cause of azotaemia by Sanguinetti (1934); other authors who have regarded the blood as an important source of nitrogen are Ingegno (1935), Borst (1938), and Schiff, Stevens, Goodman, Garber, and Lublin (1939). Hesser (1933) has shown that the passage of intestinal contents after gastro-duodenal haemorrhage is slower than normal; the time taken for barium emulsion to pass through was 8 to 14 days in most cases and in some cases as much as six weeks. This would afford ample opportunity for absorption to take place. The importance of blood in the bowel as a source of nitrogen depends on the amount of nitrogen in the shed blood, and on the rapidity with which it can be absorbed. Harrison (1939) gives the total nitrogen of blood as 3 gm. per 100 c.c., so that a haemorrhage of 1·5 litres would contain 45 gm. of nitrogen. An average day's diet contains about 1 gm. of protein per kilogramme of body weight, that is, approximately 70 gm. of protein or 11 gm. of nitrogen. A large haemorrhage may thus contain as much nitrogen as four days' normal diet. Pflüger (1909) states that 1·4 gm. of protein per kilogramme of body weight represents a maximal absorption from the bowel in an hour, and in a man weighing 70 kg. this amounts to 98 gm. of protein or 16 gm. of nitrogen. Although Pflüger's estimate is a maximal one, it shows that absorption of protein material from the bowel is a mechanism adequate to produce a rapid supply of nitrogenous material to the blood.

The effect on the blood-urea of nitrogenous absorption from the bowel is modified in various ways. In the first place, time must elapse before the protein is broken down into its constituent amino-acids. Lecoq (1937) showed that the giving of urea to healthy subjects produced a rise in blood-urea of 40 to 50 mg. per 100 c.c. in one hour, whereas amounts of dried muscle or muscle peptone containing the same quantity of nitrogen produced

a rise of only 10 mg. in two hours; peptone caused a rather more rapid increase in blood-urea than did dried muscle. Secondly, conditions for absorption may be much less favourable in patients with haematemesis than in the healthy cats on which Pflüger's estimate was based; in some cases, for example, melaena may hurry the blood through the small bowel into the colon, where absorption will not take place. Even after absorption of amino-acids has occurred, the effect on the blood non-protein nitrogen is sensibly diminished by an increased urinary excretion of nitrogen (Veraguth, 1897) and by the rapidity with which the tissues fix a large proportion of the circulating non-protein nitrogen (Cathcart, 1921). The rise in blood non-protein nitrogen after massive protein feeding, although definite, is not of the same order as that seen after gastro-duodenal haemorrhage (Pepper and Austin, 1915). Lastly, there is some further delay involved in the conversion of amino-acids to urea in the liver. Witts (1929) found that after the ingestion of 25 gm. of glycocoll the peak of blood-urea did not occur until more than an hour after the maximum level of blood amino-acid.

The results of Schiff, Stevens, Goodman, Garber, and Lublin (1939) show that large amounts of blood given to normal subjects will produce a rise in blood-urea similar to that seen after gastro-duodenal bleeding of moderate severity; and Black and Leese (1940) have demonstrated that a large part of the nitrogen of the effused blood is in part absorbed in patients with melaena. It is therefore probable that a great increase in the nitrogenous absorption from the bowel is in part responsible for the moderate rise in blood-urea which is found in most patients with gastro-duodenal haemorrhage. On the other hand, the various factors which modify the effect of massive protein feeding on the blood-urea make it unlikely that absorption of nitrogen from the effused blood can account either for a rise of blood-urea to 80 mg. per 100 c.c. or more, in a few hours, or for the values of over 200 mg. per 100 c.c. which have often been recorded in the more severe cases of haematemesis and melaena.

Katabolism of tissue protein. It might be thought that in the presence of an obvious source of nitrogen such as the blood in the bowel it was unnecessary to consider the body tissues as an alternative site of protein breakdown. We have seen, however, that the blood in the bowel does not come into operation as a source of nitrogen for some hours, whereas a rise in blood-urea may be observed within two hours of the onset of bleeding; and likewise the early elevation of blood-urea cannot be caused entirely by suspension of kidney function, as even in complete anuria after poisoning by mercuric chloride the blood-urea takes several days to reach a height which it may attain in a few hours after gastro-duodenal bleeding (Gatewood and Byfield, 1923). Moreover, azotaemia occurs in conditions such as intestinal obstruction and persistent vomiting or diarrhoea, in which the tissue proteins represent the only possible source of non-protein nitrogen. These considerations suggest that increased breakdown of tissue protein may play some part in producing azotaemia after haematemesis. It is very difficult to obtain direct evidence

of increased protein katabolism, as the amount of extra protein which must be broken down to give a rise of 50 mg. per 100 c.c. in the blood-urea is quite small, about 80 gm. As a rule, increased breakdown of tissue protein would be reflected in a negative nitrogen balance, but in these patients this method of approach is invalidated by the intake from the effused blood of a large amount of nitrogen, of which only an approximate estimate can be made. There is some indirect evidence of accelerated protein katabolism, such as increased excretion of inorganic sulphur and phosphorus, creatinuria, and loss of weight, even in patients who are not dehydrated. The observation of Black (1940 *a*) that the basal metabolism in patients with haematemesis is normal does not exclude an increase in protein katabolism, for Ashworth and Cowgill (1938) have shown that the basal metabolic rate bears no relation to the endogenous nitrogen output. In different circumstances the caloric requirements of the body are met in varying proportion by the breakdown of protein and of other foodstuffs; increase of protein katabolism in the presence of a constant basal metabolic rate means that the same caloric requirements are being met by protein to a greater extent than before. On account of the difficulties attending balance experiments in these patients, it is not possible to arrive at a quantitative estimate of the amount of tissue protein which is broken down; it is also difficult to decide the cause of protein breakdown, as several factors are present, each of which is competent to cause increased protein katabolism.

Water and salt deficiency. Patients with gastric or duodenal haemorrhage may lose well over 1 litre of body fluid in the effused blood alone, and later on 'forced diuresis' may lead to further loss of fluid; in a few patients the fluid loss may be increased by vomiting or by the presence of fever which increases loss of fluid from the skin and lungs. At the same time, they may be subjected to starvation, and, even more important, to gross restriction of the fluid intake, although the teaching of Meulengracht is leading to the adoption of a more liberal regimen for these patients. The chloride and bicarbonate content of the plasma is usually normal when the azotaemia is at its height, unless vomiting is very severe; it is therefore unlikely that there is a greater deficiency of electrolytes than of water, or vice versa. Azotaemia occurs both in water deficiency (Straub, 1899; Bang, 1916; MacKay and MacKay, 1924) and in salt deficiency (Glass, 1932; McCance, 1936), though if special precautions are taken to maintain the water content of the body, azotaemia in salt deficiency is slight (Kirsner and Knowlton, 1941).

Even in those patients with alimentary haemorrhage in whom blood-volume is not greatly reduced, the presence of haemodilution bears witness to an extensive withdrawal of fluid from the tissues. This mobilization of the tissue reserves of fluid and electrolytes is usually sufficient in amount to affect intracellular as well as extracellular fluid, for Borst (1938) has found a greatly increased potassium excretion after haematemesis, and Gamble, Ross, and Tisdall (1923) have shown that this is generally associated with

loss of intracellular fluid, which has a high potassium content. Protein in the tissues is known to be intimately associated with intracellular water, and the work of McMaster and Parsons (1939) showed that the amount of free fluid in normal tissues was so small that it could not be detected by vital staining methods. If 'bound water' is removed from a gelatin gel, damage to the protein results (Moran, 1926), and a forced removal of water from the tissues may be the ultimate cause of protein breakdown in more than one type of extrarenal azotaemia. Changes in the salt content of the tissues may also have an important bearing on the physicochemical state of tissue protein; Hardy (1905) has demonstrated the effect of sodium chloride in determining the amount of protein which will be stable in colloidal solution.

Circulatory changes and tissue anoxia. After any severe haemorrhage patients suffer both from deficiency in blood-volume and from anaemia. The initial response to diminished blood-volume is a widespread vasoconstriction, so that for a time blood-pressure is maintained, but at the cost of a greatly diminished peripheral blood flow; Gesell (1919) found that a 10 per cent. reduction of blood-volume caused the blood flow through the submaxillary gland to be diminished by more than 60 per cent. Later, if blood loss continues, the compensation by vasoconstriction fails, and the blood-pressure drops, causing a further reduction in the peripheral blood flow. Aschenbrenner (1934) has found electrocardiographic changes in haematemesis similar to those seen in patients with cardiac ischaemia secondary to coronary thrombosis, while Black, Powell, and Smith (1941) have found evidence of great reduction in the blood flow through the kidneys. Since both the volume flow and the oxygen capacity of the blood are notably reduced in these patients, the amount of oxygen carried to the tissues in any given time is much smaller; this may be compensated for to some extent by increased desaturation of the venous blood, which was observed in experimental haemorrhage by Gollwitzer-Meier (1928). In his experiments, however, the total amount of oxygen utilized in unit time by the animal was diminished, so that it may be inferred that the oxygen needs of the tissues were not being fully met, in spite of the more complete withdrawal of oxygen from the blood stream; moreover, Campbell (1931) states that the oxygen pressure in the tissues is diminished after haemorrhage. There are practical difficulties in the way of carrying out similar determinations on patients with haematemesis, but it is likely that in them, too, there is some degree of tissue anoxia, and it is relevant to consider what effect this may have on nitrogen metabolism. It has been found by von Terray (1897) and by Brunquist, Schneller, and Loevenhart (1924) that protein breakdown is increased in animals made anoxic by breathing an oxygen-poor mixture. Evans (1936) has shown that the increased excretion of nitrogen in anoxic animals is related to an increase in the glycogen content of the animal, and that this conversion of protein to carbohydrate is associated with hypertrophy of the adrenal cortex, and fails to occur when the cortex is ablated.

It may be recalled that Selye (1936) found adrenal hypertrophy as part of the 'alarm reaction' which was the response to many types of noxious stimuli.

Elimination of urea. We have found evidence of increased production of non-protein nitrogen both from the blood in the bowel and from the tissue protein, and several authors, such as Meyler (1936) have regarded the azotaemia of gastro-duodenal bleeding as essentially a 'Produktionsurämie'. This view is open to the same objection as the belief of Schiff, Stevens, Goodman, Garber, and Lublin (1939) that the condition may be explained entirely by the presence of blood in the bowel. The reserve of functional capacity of the kidney is great (Harrison, 1939), and the giving even of large amounts of urea does not produce a rise in blood-urea comparable to that observed in patients with a severe haematemesis; for example, in the Fowweather (1934) modification of the urea clearance test, the administration of 15 gm. of urea to a healthy subject raises the blood-urea only by about 17 mg. per 100 c.c. The rapid rise of blood-urea to high levels after haematemesis must therefore be determined in part by an impairment of kidney function. This does not necessarily mean that the excretion of nitrogen in 24 hours is less than normal, but merely that the reserve power of the kidney is encroached on, so that under the strain of a greatly increased formation of urea the kidneys are unable to maintain the blood-urea at a low level by increasing urea excretion correspondingly. Evidence of impaired renal function is found in the retention of nitrogen, in the low clearance of urea, inulin, and diodone, and possibly also in the low excretion of chloride even when the plasma chloride is raised.

Nature of the impairment in renal function. It has been suggested (Cain, 1938; Warembourg, 1938) that the renal impairment in patients with azotaemia after haematemesis is due to organic renal disease, latent under normal metabolic conditions, but unmasked by the sudden need to excrete large amounts of nitrogen rapidly. When one considers the high incidence of azotaemia in patients with alimentary haemorrhage, as compared with the infrequency of 'latent nephritis' in the general population, it is obvious that this explanation can be valid in a few cases only. Also, the urinary stigmata of organic renal disease are rarely found in these patients. Although albuminuria is not uncommon, it is no greater in amount than could be caused by interference with renal blood flow in the absence of any pre-existing lesion (Marshall and Crane, 1923). The absence of red cells from the urine is strong evidence against these patients having a latent nephritis (Addis and Oliver, 1931). Moreover, in three patients who died after gastro-duodenal haemorrhage, and had shown typical azotaemia, we could find no post-mortem evidence of organic renal disease; Bookless (1938) and Jones (1939 *a*) also found that morbid anatomical changes in the kidney were not such as to account for the azotaemia.

Harrison (1938) and Jeghers and Bakst (1938) have shown the value of the specific gravity of the urine as an indication of the type of renal damage

which is present. In the uraemic and pre-uraemic stages of chronic nephritis the patient passes large amounts of urine of low specific gravity. In azotaemia caused by 'functional renal failure' the volume of urine passed is small, but the specific gravity is high. An exception to this is found in patients with alkalosis, who have polyuria (Cooke, 1932); this impairment of concentration suggests damage to tubular function, which seems to be little affected in other types of functional renal failure.

Although alterations in plasma electrolytes can lead to profound diminution in renal function in such conditions as diabetic coma (McCance and Lawrence, 1935) and experimental sodium deficiency (McCance, 1936), we have seen that such alterations are uncommon in our type of azotaemia at the time when it is developing. Johnson (1941) could find no relation between the plasma-chloride level and impairment of renal function in patients with alimentary azotaemia. Borst (1936 *a*) and Christiansen (1937) have discussed the possibility that alterations in the secretion of certain hormones may affect kidney function in post-haemorrhagic azotaemia. The presence of a high plasma-chloride in some cases suggested an over-production of cortin, which might conceivably diminish urinary excretion of chloride, although Harrop and Thorn (1937) found that this effect was slight even with large doses of cortin. Black (1940 *b*) found that massive doses of cortin and of desoxycorticosterone did not increase the azotaemia which follows experimental haemorrhage. Attention has also been drawn to the increased production of adrenalin in haemorrhage (Heymans, Bouckaert, and Regniers, 1933); injection of adrenalin does interfere with chloride excretion, but is not sufficient in itself to diminish the excretion of urea (Frey, 1917). For these reasons electrolyte and hormone disturbances cannot be considered important causes of the renal failure.

Our own belief is that the functional failure observed in these patients is caused by a fall in the pressure and amount of the blood supplied to the kidney. Van Slyke, Rhoads, Hiller, and Alving (1934) have shown that in dogs fluctuations in the clearance of urea are closely related to changes in renal blood flow. Direct measurements of the amount of blood flowing through the kidney are not possible in patients with haematemesis, but the reduction in diodone clearance observed by Black, Powell, and Smith (1941) suggests that the effective renal blood flow is diminished. In patients with severe haematemesis, not only is the total blood-volume greatly reduced, but the blood-pressure is low. This may cause a reflex fall in the blood flow through the kidney (Bayliss and Fee, 1930), and it has long been known that a fall in blood-pressure is attended by oliguria (Goll, 1854) and diminished glomerular filtrate (Starling, 1899). A further possible cause of reduced blood flow is renal vasoconstriction. Diminution in renal blood flow causes a smaller volume of glomerular filtrate to be formed, so that for any given level of blood-urea a smaller amount of urea will be excreted by glomerular filtration. More important, the diminished volume of glomerular filtrate will lead to oliguria, since tubular reabsorption is not greatly

impaired in these patients, if one may judge by the high specific gravity of the urine. Oliguria is attended by increased re-absorption of urea by the tubules both in rabbits (Mayrs, 1922) and in man (Rehberg, 1926), so that the amount of urea in the final urine will be still further reduced. Chesley (1938) has shown that in consequence urea clearance at low urine-volumes gives an unduly low estimate of renal function. For these reasons the excretion of urea is diminished, even although the blood-urea level is high, and one would expect a raised output of urea.

It may be convenient, before considering the general significance of the azotaemia of alimentary haemorrhage, to summarize the information which we have gained as to its pathogenesis. There is good direct evidence of absorption of nitrogen from the blood in the bowel, and there is also good reason to believe that the katabolism of tissue protein is accelerated, though direct proof of this is precluded by the inherent difficulties of balance experiments in such patients. Although this increased formation of nitrogenous end-products could readily be dealt with by a normal cardiorenal system, without any gross rise in blood-urea, in the patients with whom we are dealing the kidneys are hampered by a diminished supply of blood at a reduced pressure, and are unable to excrete urea rapidly enough to prevent considerable rise in the amount of urea in the body, and thus in blood-urea concentration. In a few patients the rise in blood-urea is exceptionally great, owing to special circumstances, such as pre-existing renal disease, alkalosis due to vomiting, or gross dehydration caused by excessive fluid restriction. The rise of blood-urea in gastro-duodenal haemorrhage is higher and more prolonged than in other forms of haemorrhage, because the initial azotaemia due to the loss of blood is aggravated by the absorption within a few hours of nitrogen from the blood in the bowel; and at the same time the intake of fluid is interfered with, so that tissue dehydration persists for a longer period and the elimination of urea is impaired.

General Significance of the Azotaemia

Relation to other forms of extrarenal azotaemia. The various disease states in which azotaemia may occur apart from organic renal disease have been reviewed by Barnes and Lowe (1936) and by Jeghers and Bakst (1938). Jeghers and Bakst point out that the term 'extrarenal azotaemia', so commonly applied, is to some extent inapposite, since a functional renal impairment is often concerned in the aetiology. We have seen how difficult it is for over-production of urea to cause azotaemia if the kidneys are healthy, and it has also been noted that even complete cessation of urea elimination by the kidney takes some days to produce a severe azotaemia, whereas most forms of extrarenal azotaemia are rapid in onset. Although arguments based on analogy are dangerous in natural science, it seems most likely that just as in haematemesis, so in other forms of extrarenal azotaemia, both increased production and faulty elimination of urea must be concerned. The special feature of alimentary haemorrhage, which marks it out from

other causes of azotaemia, is that the effused blood is retained within the bowel to a large extent, and acts as an important source of nitrogen. Apart from the presence of blood in the bowel, the chief factors in causing azotaemia in alimentary haemorrhage seem to be the diminished blood-volume, and changes in the water and salt content of the tissues. Are similar factors of importance in causing other types of extrarenal azotaemia? Jeghers and Bakst (1938) claim that all the numerous types of extrarenal azotaemia 'can be explained on the basis of one or more of six fundamental mechanisms', which they give as follows:

(1) Fall in blood-pressure.
(2) Hypochloraemia and hyponatraemia.
(3) Dehydration.
(4) Increased protein katabolism.
(5) Liver damage.
(6) Local renal failure.

Although this list is of help in understanding the problems involved in the aetiology of extrarenal azotaemia, it cannot really be regarded as consisting of 'fundamental mechanisms', since most of its components can be explained on the basis either of diminished blood-volume or of electrolyte changes, or both. For example, a diminished blood-volume leads to fall in blood-pressure, renal insufficiency, and increased protein katabolism, while changes in water and salt metabolism include dehydration, hypochloraemia, and hyponatraemia, and may lead to increased protein katabolism and renal insufficiency. Even fall in blood-volume and disturbance of water and salt metabolism cannot be regarded as independent of one another, for on the one hand a fall in blood-volume occurs as a secondary phenomenon in conditions where water and salt metabolism are faulty, such as diabetic coma (Horwitz, 1931) and intestinal obstruction (Aird, 1938), while on the other hand a fall in blood-volume leads to a rapid withdrawal of fluid from the tissues into the blood-stream (Robertson, 1938), and therefore alters the electrolyte status both of blood and tissue.

It is possible that in some types of extrarenal azotaemia, as in acute fevers and peritonitis, toxic action on the tissues and kidney may play a part, but we have seen that this is of little import in haematemesis. Also, specific damage to the liver must be present in the small group of cases where the azotaemia is due mainly to residual nitrogen, and not to urea (Nonnenbruch, 1939). For the most part extrarenal azotaemia from whatever cause can be traced back to reduced blood-volume, or disturbed water and salt metabolism, or both. Either of these primary causes can produce both increased protein katabolism and functional renal failure, and it is probable that both these secondary changes must be present before azotaemia develops.

Relation of the height of azotaemia to prognosis. Although Bookless (1938) has noted restlessness, mental apathy, and coated tongue in patients with haematemesis whose blood-urea was over 190 mg. per 100 c.c., the azotaemia

of haematemesis is not usually associated with symptoms of clinical uraemia (Ingegno, 1935). It is unlikely that the azotaemia of haematemesis is harmful in itself, for the increase is almost entirely in urea, which does not seem to be responsible for the grave manifestations of nephritic uraemia (Harrison and Mason, 1937). It is generally agreed that the height of the azotaemia is related to the severity of bleeding which has occurred, and has therefore considerable prognostic significance. If the blood-urea is not raised in a patient with haematemesis or melaena, bleeding has probably ceased; whereas a high blood-urea, and especially one which repeated estimation shows to be increasing, is very suggestive of continuing or recurrent haemorrhage (Christiansen, 1937). Witts (1937) includes a blood-urea of over 100 mg. per 100 c.c. as one of the indications for transfusion. Bookless (1938) states that the blood-urea is more reliable than the haemoglobin percentage or blood-pressure as a guide to the patient's condition after severe internal haemorrhage. On the other hand, Crohn and Lerner (1939) are not so favourably impressed with the prognostic value of blood-urea figures. Of course, the blood-urea level may be affected not only by complications such as alkalosis and organic renal disease, but by the extent to which the diet allowed to the patient is adequate to prevent dehydration. If these possible modifying factors are kept in mind, and any necessary allowance made, estimations of blood-urea are of great value in judging the severity of gastro-duodenal bleeding, and in following the patient's progress.

Therapeutic implications. Although the azotaemia in gastro-duodenal bleeding does not in itself require treatment, it is symptomatic of a grave condition of the patient; and the insight which has been gained into its causes enables certain conclusions to be drawn about the treatment of patients with alimentary bleeding. While a moderate rise of blood-urea to 50 or 60 mg. per 100 c.c. may be due merely to the presence of blood in the bowel, any greater azotaemia is an indication of renal insufficiency and tissue breakdown, and treatment is indicated to improve kidney function, and to prevent further tissue wasting. Even if absorption of nitrogen from the blood in the bowel were known to be harmful, nothing could be done to prevent it; for while some might admire, few would emulate the therapeutic enthusiasm of Sanguinetti (1934), who advocated caecostomy in order to get rid of stagnating blood. It is more important and more practicable to restore a diminished blood-volume, and to prevent fluid and electrolyte depletion, which we have found to be important causes of azotaemia.

Restoration of blood-volume. The obvious method of restoring blood-volume in patients with haematemesis is by transfusion of whole blood. In the past there has been reluctance to transfuse patients with bleeding peptic ulcer, on the ground that a rise in blood-pressure may follow and increase the severity of the bleeding. This risk does not appear to be present if blood is given by the slow drip method of Marriott and Kekwick (1935), for with this method not only is there no rapid rise in blood-pressure, but the systolic pressure may actually diminish. If the blood-pressure is greatly reduced

before transfusion, a rise in blood-pressure occurs even when the blood is dripped in slowly, but it is a gradual increase, and the risk of its producing renewed haemorrhage is less than the risk of allowing a dangerously low blood-pressure to persist for hours. The effect of transfusion on blood-pressure in these patients has been fully dealt with by Jones (1939 *b*).

The amount of blood which may be lost in bleeding from peptic ulcer varies greatly from one patient to another, and it is often difficult to estimate clinically how severe the bleeding has been, for the rapid loss of a small amount of blood may produce as much appearance of circulatory failure as a larger but more gradual haemorrhage. It is impossible to estimate the blood-loss from the amount of vomited material, as this consists partly of gastric juice; also, only part of the effused blood is vomited. Estimations of blood-volume, while they constitute a good method of assessing blood loss in these patients, cannot be used as a clinical routine measure, as the method though simple is time-consuming. It is therefore important to have some practical criteria as to when blood should be given. Witts (1937) considers that transfusion is indicated by a blood-urea of over 100 mg. per 100 c.c., a pulse-rate of 140 or more, a systolic blood-pressure of less than 90 mm., or a haemoglobin of less than 40 per cent. We have now had considerable experience in the use of these indications, and have not had occasion to regret the giving of transfusions on this basis.

There are at present three main types of blood derivatives which are generally available for transfusion:

(1) Citrated whole blood.

(2) Plasma or serum, which do not differ significantly from each other in their action as blood substitutes (Best and Solandt, 1940).

(3) Concentrated red-cell suspension, obtained by pipetting off the plasma from sedimented citrated whole blood (MacQuaide and Mollison, 1940).

Since it is whole blood which is lost in gastro-duodenal haemorrhage, citrated whole blood would seem to be indicated as the standard transfusion medium for these patients. Are there any circumstances in which plasma or serum on the one hand, or red-cell suspension on the other, offer any advantage in the treatment of gastro-duodenal haemorrhage? It is well known that serum and plasma are efficient agents in the treatment of surgical shock, particularly when this is not associated with gross haemorrhage. Even in haemorrhage good results have been obtained with plasma, both in animals (Magladery, Solandt, and Best, 1940) and man (Brennan, 1940). There is a stage soon after severe haemorrhage when the blood-volume is reduced, without any lowering of the haemoglobin percentage; if haemorrhagic shock is severe, restoration of blood-volume by the passage of fluid from tissues to blood-stream is delayed, and a transfusion of plasma should improve the circulation by increasing the blood-volume. It must be emphasized that the stage of diminished blood-volume, with normal haemoglobin percentage, is usually transient, and Magladery, Solandt, and Best (1940) obtained the best results with plasma and serum when these were

given as soon as possible after the experimental haemorrhage. It is possible that immediately after a severe and sudden gastro-duodenal haemorrhage there might be some indication for plasma, but in practice patients with haematemesis are seldom transfused until some hours after the bleeding, by which time blood dilution has occurred. Black and Smith (1941) found that in the treatment of patients with alimentary haemorrhage plasma was not only inferior to whole blood in its effect on azotaemia, but also, by aggravating the anaemia, it might cause a dangerous deterioration in the general state of the patient.

The use of a concentrated suspension of red cells is indicated only when one wishes to increase the haemoglobin percentage with the smallest possible change in total blood-volume. A red-cell suspension can be given as rapidly as whole blood, with equal safety, and the rise in haemoglobin produced by any given volume transfused will be much greater. There is therefore scope for the transfusion of red cells in those cases where anaemia, with a haemoglobin of 40 per cent. or less, is the chief indication for transfusion. A day or two after severe alimentary haemorrhage, it is usual to find that the blood-volume has been made up to normal by dilution with tissue fluid, so that the haemoglobin percentage is greatly reduced. Such patients require transfusion, since any recurrence of haemorrhage at a low haemoglobin level is likely to be fatal. In these patients transfusion of concentrated red cells has the advantages over whole-blood transfusion that a smaller volume of transfused material will produce the same increase in haemoglobin, and that the plasma separated from the red cells can be stored for use in shock treatment.

In a severe case of bleeding from peptic ulcer the blood-volume is depleted by 1 litre or more, and 1 litre may be regarded as the average amount of blood which should be given for a single large haemorrhage. Usually a considerable improvement in the patient's general condition is manifest during the actual course of the tranfusion, and blood up to 1 litre should be administered until a favourable response is obtained. After 1 litre of blood has been given, the possibility of over-transfusion of the patient must be kept in mind, and the transfusion should be continued only if the blood-pressure is still low and the arm veins collapsed, indicating that the blood-volume is still diminished. The appearance of venous engorgement is an early and definite indication for stopping the transfusion. In the presence of continued bleeding very large amounts of blood may have to be given before a rising haemoglobin percentage indicates that progress is being made; Jones (1939 *b*) tells of three patients who recovered after each had received more than 6 litres of blood. The rate at which the blood is administered is of the greatest importance; 1 litre of blood should not be given in less than eight hours, and the rate may well be slower still. A slow transfusion rate is necessary to avoid a sudden rise in blood-pressure, which might break down incipient haemostasis at the site of bleeding. The need for slow transfusion in these patients stands in contrast to patients with wound shock, in whom

all are agreed that rapid tranfusion is both safe and necessary. The essential difference between the two types of patient is that in wound shock the site of haemorrhage can be directly controlled by surgical means, and there is no contra-indication to restoring the blood-volume to full normal limits, whereas in gastro-duodenal haemorrhage the bleeding-point is inaccessible, and haemorrhage might easily be aggravated by the plethora which follows the rapid transfusion of large amounts of blood.

If transfusion is used in response to definite indications, and reasonable principles adopted with regard to the amount of blood given and the rate of administration, the results are very good. The effect of transfusion in lessening tissue breakdown and improving kidney function is shown by a rapid fall in blood-urea; more direct evidence of an improvement in renal function is given by a notable increase in urea and inulin clearance. A fall in pulse-rate is commonly observed, the haemoglobin percentage and blood-volume increase, and the blood-pressure, if reduced before transfusion, returns to normal values. Clinically, pallor and weakness diminish, the skin becomes warm, and it is common to see a restless and anxious patient become quiet and composed during the course of a transfusion.

Maintenance of fluid balance. A normal person of average size requires some 2·5 litres of fluid per diem to balance the output in urine and stools and from the skin and lungs. In a patient with haematemesis, the loss of fluid from the skin is commonly increased by sweating, while the large excretion of urea in the days following the bleeding produces a forced diuresis (Jones, 1939 *a*). If these additional losses of fluid are taken into account, the fluid requirement of a patient with haematemesis must be in the region of 3·5 litres per diem, a figure which corresponds to the estimate of Coller (1936) for sick patients in general. In addition, from 2 to 3 litres of fluid are lost at the onset by bleeding and by vomiting of gastric secretion. It is not difficult to see why patients treated by rigorous limitation of food and fluid intake became 'dehydrated, dirty-tongued, collapsed and semi-uraemic', and in the days when little if any fluid was given by mouth, it was often necessary to give saline infusions on account of the severe dehydration which developed (Christiansen, 1937). Jones (1939 *a*) gives figures which show the extent to which starvation treatment caused negative fluid balance, and the extreme degree of dehydration which was produced thereby. One ought therefore to give these patients an allowance of 3 litres of fluid per diem, leaving 500 c.c. to be accounted for by water of oxidation of the diet. Since water without salt will not be retained in the body, one must give also about 10 gm. of sodium chloride per diem. Now, it is quite possible to give large amounts of fluid intravenously, and a rather less amount by rectal drip, but intravenous therapy demands daily control by laboratory estimations of chloride and bicarbonate, if one is to control dehydration properly, and at the same time avoid the risk of pulmonary oedema. Moreover, it is quite unnecessary to subject these sick patients to the discomfort of a continuous intravenous or rectal drip, if the

principle be accepted that it is safe to give fluid by mouth right from the onset of treatment. Treatment by early feeding, although introduced by Lenhartz, has found its most persistent advocate in Meulengracht (1933, 1934, 1935, 1936, 1937, 1939). The arguments in favour of early treatment with food, as opposed to initial starvation, have been fully dealt with by Meulengracht himself, and by Witts (1937). In summary, early feeding is well liked by the patients, and avoids dehydration and exhaustion; there is no greater risk of recurrent haemorrhage, blood regeneration is more rapid, and mortality figures are lower. It is probable that the chief value of the method lies in the principle of giving something right from the start, and that no special virtue attaches to the type of food which is given; Meulengracht's own results were obtained with a diet which many would consider unduly venturesome for the treatment of ulcer patients, but a bland fluid or semi-fluid diet, such as Sippy II diet, gives good results. In this diet the total fluid intake averages about 2,750 c.c., and this is increased by water of oxidation. The daily requirement of 10 gm. of sodium chloride can be met by giving 1,500 c.c. of half-strength saline as part of the diet, and by adding salt to the feeds (Jones, 1939 *a*). Although the fluid and salt content of the diet are the important factors in preventing dehydration, the calories and vitamins must also be adequate.

Summary

1. In patients with severe bleeding into the stomach or duodenum, from whatever cause, the blood-urea is almost constantly raised. As a rule the increase is moderate in degree, to about 70 mg. per 100 c.c., but much higher values have frequently been observed. The rise in blood-urea may be present within two hours of haemorrhage, and is at its height on the day after the haemorrhage, falling to a high normal level in the next two or three days, and to completely normal figures in a week or ten days. If haemorrhage is severe, the rise in blood-urea is greater, and recurrence of bleeding is attended by a secondary increase in blood-urea.

While azotaemia in gastro-duodenal bleeding is almost entirely accounted for by the increase in blood-urea, the amino-acid nitrogen is also slightly raised, but creatinine and uric acid are normal. Plasma-chloride, bicarbonate, and total base show no constant change; chloride may be high or normal at the time of maximal azotaemia, and diminishes during the days after haemorrhage. The blood-volume is usually, but not always, diminished, and may be less than half the normal amount; anaemia and leucocytosis are present. The volume of urine passed is diminished for 24 to 48 hours after the haemorrhage, but thereafter excretion of urea causes a 'forced diuresis'. The specific gravity of the urine is normal or even high, and the urea concentration is good. Urinary chlorides are very low. Albumin and casts may be found in the urine of a few patients. The clearance of urea, inulin, and diodone is diminished when the blood-urea is rising, but may later be normal. Metabolic experiments show that large amounts of nitrogen are absorbed

from the blood in the bowel; for this reason, the nitrogen balance is positive, even although loss of weight, creatinuria, and increased excretion of inorganic sulphur and phosphorus suggest that tissue protein is being broken down at an increased rate.

After external haemorrhage in man or animals the blood-urea may be unchanged, or moderately increased, depending on the severity of the haemorrhage. The giving of large amounts of blood by mouth causes a rise in the blood-urea, though this is both smaller and slower in onset than the azotaemia of severe haematemesis. Anaemia in itself causes little increase in blood-urea, and shock and vomiting in patients with haematemesis are rarely severe enough to determine the occurrence of azotaemia.

2. *Causes of the azotaemia.* There is an absolute increase in the urea content of the body, which may be caused either by increased formation or decreased excretion of urea, or by both.

(a) *Increased formation of urea.* Although absorption of nitrogen from the blood in the bowel occurs in patients with gastro-duodenal bleeding, it cannot account for a very rapid or a very severe azotaemia. The fact that azotaemia occurs in such conditions as fever or alkalosis, where there is no question of large amounts of nitrogen being absorbed from the bowel, suggests that increased breakdown of tissue protein may be present in haematemesis as well. Increased tissue breakdown may be caused either by loss of body fluid or by circulatory changes which produce tissue anoxia.

(b) *Decreased elimination of urea.* Evidence of renal failure is afforded by the azotaemia itself, by diminished water and salt excretion, and by a fall in urea, inulin, and diodone clearance. Anatomical renal damage is found only occasionally in these patients, and the high specific gravity of the urine shows that there is no gross impairment of tubular function. On the other hand, there is a pronounced fall in glomerular filtration, and the renal plasma flow is diminished by the low blood-volume and blood-pressure, and possibly also by renal vasoconstriction. The amount of urea excreted is reduced not only by the fall in glomerular filtration, but by the increased tubular reabsorption of urea which takes place at low urine-volumes.

The available evidence suggests that the usual moderate rise in blood-urea is accounted for mainly by absorption of nitrogen in large amount from the blood in the bowel at a time when the kidneys are hampered by a diminished volume-flow of blood. If the haemorrhage is unusually severe, breakdown of tissue protein becomes important as a source of nitrogen, and kidney function is further impaired, so that the azotaemia is more pronounced. In a few patients special circumstances such as pre-existing renal disease, alkalosis due to vomiting, or gross dehydration caused by excessive fluid restriction, lead to blood-urea values of 200 mg. per 100 c.c. or more.

3. *Significance of the azotaemia.* (a) *Extrarenal azotaemia in general.* The rise in blood-urea after severe haematemesis seems to depend on a combination of reduced blood-volume and changes in water and salt metabolism; a survey of the causes of extrarenal azotaemia shows that one or other of

these factors is almost constantly present, though in some types of extrarenal azotaemia liver damage may play a greater part than it does in haematemesis. It is probable that fall in blood-volume and changes in fluid-balance act in a similar way in the different types of extrarenal azotaemia, so that the detailed information which has become available about their mode of action in alimentary haemorrhage may have relevance in other forms of azotaemia as well.

(b) *Prognosis and treatment.* The height to which the blood-urea rises is of value in judging the severity of gastro-duodenal haemorrhage, and repeated estimations afford a good measure of progress. Although the azotaemia is not in itself harmful, its presence indicates renal failure and increased tissue breakdown which demand treatment directed towards restoring the blood-volume and maintaining the fluid-balance. Restoration of blood-volume by transfusion is indicated by a blood-urea of over 100 mg. per 100 c.c., as well as by a pulse-rate of over 140, haemoglobin of less than 40 per cent., or systolic blood-pressure of less than 90 mm. In an average case 1 litre of blood should be given by slow drip. When the haemoglobin is low, and the blood-volume normal, the use of sedimented red cells in place of whole blood may be of advantage; patients with gastro-duodenal haemorrhage show a very unfavourable response to plasma transfusion. From the very commencement of treatment fluid-balance should be maintained by a diet which allows about 3 litres of fluid and 10 gm. of sodium chloride per diem.

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CHRONIC PEPTIC ULCER OF THE OESOPHAGUS AND ITS ASSOCIATION WITH CONGENITALLY SHORT OESOPHAGUS AND DIAPHRAGMATIC HERNIA[1]

By R. C. S. DICK and ARTHUR HURST

With Plates 2 to 4

Chronic peptic ulcer of the lower end of the oesophagus was regarded until recently as a pathological curiosity. Stewart (Hurst and Stewart, 1929) observed a single case in over 10,000 consecutive post-mortem examinations at Leeds, and in 1906 Tilestone was able to collect only eight cases from the literature. Twenty-three years later Hurst and Stewart (1929) collected 11 more, excluding a remarkable series observed by Jackson (1929) who in the course of 42 years had seen 21 active ulcers and 67 scars of healed ulcers in 4,000 oesophagoscopic examinations. Jackson thought that the routine use of the oesophagoscope in cases of slight dysphagia, pain behind the sternum, and haematemesis of obscure origin would show that the condition is much less rare than had hitherto been believed. Friedenwald, Feldman, and Zinn came to the same conclusion in 1929, when they published records of 13 cases from their own practice in which the diagnosis had been confirmed by X-rays and oesophagoscopy. With this opinion we now fully agree, as we have seen 16 private cases and a rather smaller number at Guy's Hospital and the Radcliffe Infirmary since 1933. In agreement with these clinical observations are the pathological observations of Lyall (1936), who found eight chronic oesophageal ulcers in 1,500 post-mortem examinations at Glasgow between 1932 and 1936. Chronic oesophageal ulcer is in fact a comparatively common disease with very characteristic symptoms and characteristic radiographic and oesophagoscopic appearances. In spite of this, although we had long been interested in the subject of gastric and duodenal ulcer, we had never recognized a case of oesophageal ulcer clinically until 1933.

The hernia of part of the stomach into the thorax through the oesophageal hiatus which results from congenital shortness of the oesophagus has been familiar for many years to radiologists, but it has generally been thought to be of little clinical importance. In 1935 we observed a diaphragmatic hernia of this kind associated with a chronic oesophageal ulcer. Since then more careful investigation has demonstrated that the latter rarely occurs without the former, although the reverse is, of course, not true. Our third case was first seen in September 1936 with Dunhill, who had recently (1935) recorded

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the fact that an oesophageal ulcer was present in two of the 14 cases which he had seen of diaphragmatic hernia associated with a short oesophagus. This association was described by us with Briggs (Hurst, Briggs, and Dick, 1939). At that time we were unaware that it had been previously observed except by Dunhill, but we have now discovered a reference to a single case by Haroen and Gerlings dating from 1934, and a description of two cases by Feldman (1939) which appeared simultaneously with our communication. Still more recently Johnstone (1941) has reported seven cases of chronic oesophageal ulcer, all of which were associated with a short oesophagus. The case described by Haroen and Gerlings (1934) was that of a child of three who had vomited blood-stained material at frequent intervals since she was a week old. X-rays showed that she had a diaphragmatic hernia of her stomach with a congenitally short oesophagus, and that an ulcer was present at its lower end (Plate 2, Fig. 3). The diagnosis was confirmed by oesophagoscopy.

Aetiology

Sex. The sex incidence of chronic oesophageal ulcer showed a male preponderance of about 3·5 to 1 in the 19 cases collected by Hurst and Stewart (1929), and there were five men to three women in Lyall's (1936) eight cases. On the other hand, there were seven women to six men among Friedenwald, Feldman, and Zinn's (1929) 13 cases, and no less than 12 women to four men among our 16 private cases. When these figures are combined together, it is seen that the incidence in males and females is approximately the same.

Age. The age at onset of symptoms in our four men was 22, 58, 65, and 72 years, and in our 12 women 18, 25, 29, 35, 37, 37, 40, 46, 48, 50, 53, and 76 years. These patients were first seen by us at the age of (men) 62, 66, 68, and 78, and (women) 52, 40, 35, 68, 57, 50, 74, 56, 55, 65, 63, and 76 years, that is after intervals varying between nine months and 40 years, with an average of 17 years. The age at onset of symptoms in Friedenwald, Feldman, and Zinn's series was approximately the same as in ours, 20, 31, 33, 41, 41, 46, 47, 50, 50, 53, 54, 58, and 64 years.

Morbid Anatomy

The morbid anatomy of chronic peptic ulcer of the oesophagus differs in no way from that of chronic gastric and duodenal ulcer, but as seen at autopsy the details are liable to be more obscured by post-mortem changes. The ulcer is generally single; more than one was present in only three of Jackson's 21 cases of active ulceration examined with the oesophagoscope. The ulcers are always situated in the lower third of the oesophagus, generally immediately above the sphincter. Their size varies from a tiny lesion a few millimetres in diameter to one completely encircling the lumen. Small ulcers are round or oval; larger ones tend to be irregular and are often annular. The wall is penetrated to a variable depth with exposure or perforation of the muscular coat; the margins are usually clean-cut and may be undermined. From the floor and margins fibrosis extends outwards to involve

adjacent structures, which become firmly adherent to the oesophagus. Judged by the relative frequency of the evidence of scarring as opposed to that of active ulceration found clinically as well as *post mortem*, the usual course for a chronic oesophageal ulcer is to heal completely. In Stewart and Hartfall's (1929) case a large well-healed scar was present on the anterior wall in addition to an active ulcer directly opposite, and several similar cases have been reported. Jackson (1929) was able to demonstrate scars of healed ulcers in 67 cases compared with only 21 active ulcers. Complete healing may occur without any obstruction developing, but stenosis of varying degrees frequently results.

Pathogenesis

The acid factor. Chronic ulcers of the kind found in the stomach and duodenum occur only in those parts of the alimentary canal which are exposed for long periods to the action of gastric juice. Thus they never develop in the dome-like roof of the fundus, which normally contains air and not acid chyme, nor in the duodenum beyond the bulb, which is the only part in which the contents are frequently acid. They may also develop just beyond the anastomosis after gastrojejunostomy and partial gastrectomy, if free hydrochloric acid is still present after the operation. It might therefore be expected that the otherwise indistinguishable chronic ulcers found in the lower end of the oesophagus should also be 'peptic' and associated with the unaccustomed presence of gastric juice containing free hydrochloric acid. If this is true, it would explain why a chronic ulcer has never been found in association with achalasia of the cardiac sphincter in spite of the constant presence of chronic oesophagitis, the mixture of food, saliva, and mucus in the dilated oesophagus being always alkaline.

The mucous membrane at the cardia shows a very abrupt change from the stratified squamous epithelium of the oesophagus to the simple columnar epithelium of the stomach. This is well seen in Plate 2, Fig. 4, reproduced from Lendrum's (1937) recent study of the anatomy of the cardiac orifice. It is easy to understand how little the lining epithelium of the oesophageal mucous membrane is able to withstand the peptic activity of the gastric juice, which bathes the gastric mucosa with impunity. In four out of our five patients who were given a test-meal hyperchlorhydria was present; in the fifth there was a high normal curve. This suggests that there is a special liability of patients with constitutional hyperchlorhydria to develop oesophageal ulcer, which is probably the result, as in duodenal and anastomotic ulcers, of the increased corrosive action of the more concentrated acid, as the digestive power of the pepsin of the gastric juice does not increase with a rise in the quantity of free hydrochloric acid above the average normal. The association with constitutional hyperchlorhydria is further shown by the fact that a gastric or duodenal ulcer was found in 10 out of 24 recorded autopsies on patients with chronic oesophageal ulcer. Gastric juice gains access to the lower end of the oesophagus as a result of regurgitation from the stomach through an incompetent cardia associated with a congenitally

short oesophagus, and much less frequently owing to its secretion by islands of ectopic gastric mucosa in the oesophagus.

Regurgitation of gastric juice into a congenitally short oesophagus. Congenital shortness of the oesophagus is a result of its failure to elongate with sufficient rapidity to keep pace with the growth in length of the embryo. A portion of the stomach is consequently pulled up from below the septum transversum to form a true hernia. The elongation of the oesophagus is most active in the 5 to 10 mm. embryo during the fourth and fifth weeks, and it is therefore likely that the hernia dates from this very early stage of development.[2]

When the act of swallowing is watched with the aid of X-rays the opaque food is seen to pass rapidly down the oesophagus as far as the entrance to the cardiac sphincter, where there is a momentary pause before the sphincter relaxes and allows the passage of the food into the stomach. We observed a similar pause above the closed sphincter in cases of congenitally short oesophagus, whether associated with a chronic peptic ulcer or not. The investigations of Hurst (1914) and Hurst and Rake (1929) on achalasia of the cardiac sphincter demonstrated that the tone of the closed sphincter can resist a pressure from above of 6 to 8 in. of water. Under normal conditions this pressure does not overcome the resistance offered at the cardia to the passage in the reverse direction of the contents of the stomach into the oesophagus, but it is quite sufficient when a congenitally short oesophagus has led to a portion of the stomach becoming displaced into the thorax. Thus the increase in the intragastric pressure at the level of the cardia, which occurs on lying in the supine position, though sometimes only after compression of the abdomen with the hand, and on leaning forward in the erect position, is sufficient to cause regurgitation of the contents of the stomach into the oesophagus if the latter is congenitally short, but such regurgitation never occurs into a normal oesophagus. Drs. Briggs and Dick watched a patient with an oesophageal ulcer and short oesophagus whose stomach was full after an opaque meal. While she was prone, each inspiratory excursion of the diaphragm was accompanied by aspiration of food into the thoracic portion of the stomach and each expiration expelled it back into the abdominal portion, but there was no regurgitation into the oesophagus. When she turned on to her back so that the intragastric pressure below the cardia increased by an amount equal to a column of water the thickness of the abdominal cavity, the opaque material no longer left the thoracic portion of the stomach on expiration, and some of it immediately ran up the oesophagus into the mouth. Clearly the cardiac sphincter of the short oesophagus, though closed at rest, can, in contrast with that of the normal oesophagus, be forced as easily from below as from above. This difference between the short and the normal oesophagus depends not upon any difference in the behaviour of the cardiac sphincter, but on the loss when it is in the thorax of the valvular

[2] We are indebted to Mr. P. N. B. Odgers for this explanation of the development of congenital shortness of the oesophagus.

mechanism which exists at its lower extremity, the actual 'cardia',[3] when it is normally situated in the abdomen. The left or upper half of the wall of the lower extremity of the oesophagus forms an acute angle where it meets the inner wall of the fundus of the stomach, whereas the right or lower half forms an obtuse angle with the upper end of the lesser curvature. The acute angle is maintained and strengthened by the ∩-shaped band of oblique muscle fibres, which Lendrum (1937) showed pass upwards from each side of the lesser curvature of the stomach to fuse above the left aspect of the cardia (Plate 2, Fig. 5). A valve is thus formed, which offers no resistance

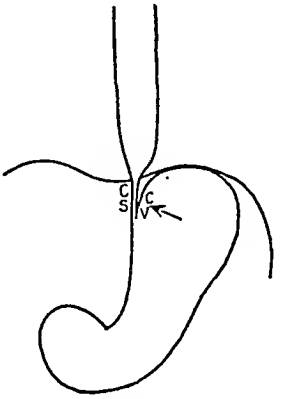

FIG. 1

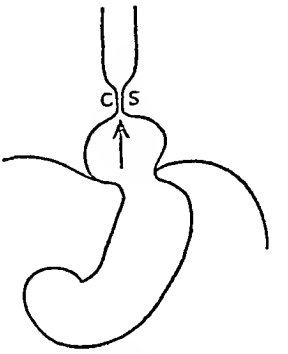

FIG. 2

CS, cardiac sphincter; CV, cardiac valve

to the passage of food from the oesophagus into the stomach when the cardiac sphincter relaxes, but prevents regurgitation from the stomach by means of the flap formed by the left upper wall of the lower extremity of the oesophagus being pressed against the right lower wall when the intragastric pressure is raised (Fig. 1).

When a portion of the stomach is present in the thorax owing to congenital shortness of the oesophagus, the latter joins the top of the thoracic portion of the stomach, which is arranged evenly around it in contrast with the normal angular junction (Fig. 2). The valvular mechanism at the cardia is therefore lost and no resistance is offered to the regurgitation of the stomach contents into the oesophagus when the thoracic portion of the stomach is filled and the pressure at the cardia is increased sufficiently to force the closed sphincter.

The combination of a sphincter with a valve at the cardia has a counterpart at the ileocaecal junction. In 1590 Bauhin found that the ileocaecal valve resists a moderate degree of pressure from the side of the colon, but very little from that of the ileum. The existence of a true ileocaecal sphincter was proved by the anatomical observations of Good (1822), Keith (1903), and Rutherford (1914), and the physiological observations of Elliott (1904), and of Hurst and Newton (1913).

[3] The cardia is the point where the oesophagus joins the stomach, that is, the lower extremity of the cardiac sphincter, to which its relation is the same as that of the pylorus to the pyloric sphincter and the anus to the anal sphincter.

Johnstone (1941)[4] has recently described seven cases of chronic oesophageal ulcer, in all of which there was definite shortening of the oesophagus. He regards the short oesophagus as secondary to cicatricial contraction of the ulcer and not, as we maintain, the predisposing cause. The main reason for this appears to be that in his experience oesophageal ulcer occurs only late in life, the average age in his cases being 64 years. It might be expected to develop earlier with a congenital abnormality, but the average age at the onset of symptoms in the 12 of our 16 private cases in which a short oesophagus was certainly associated with the peptic ulcer, varied between 18 and 76 with an average of 44 years. Although several patients had had symptoms for many years when they were first seen by us and the short oesophagus discovered, in one the symptoms had been present for only a few months. Our oldest patient, a man of 78 years, who had had symptoms of oesophageal ulcer for six years, finally developed a severe fibrous stricture. His case was therefore one in which shortening of the oesophagus might have been expected to occur as a result of cicatricial contraction, if this ever really takes place, but he was one of the few cases in our series in which the ulcer was not associated with shortening of the oesophagus, as no hernia of the stomach into the thorax was present. The symptoms in the three-year-old child observed by Haroen and Gerlings (1934) began when she was only a week old, so that in this case at least the short oesophagus was almost certainly congenital. Moreover, if sufficient cicatrization occurred to pull a portion of stomach out of the abdomen into the thorax, it might be expected to cause stenosis of the comparatively narrow oesophageal lumen at the same time, but in most of our cases none was present. Dysphagia was often absent, and when present it was generally the result of spasm, as it disappeared when the ulcer healed. The fibrous tissue produced when an oesophageal ulcer heals tends to anchor it to the surrounding parts, so that it would be very unlikely to be displaced upwards and to draw some of the fundus of the stomach out of the abdomen. Moreover, the normal oesophagus is not taut in a longitudinal direction, as it is easy to pull an inch or more of the thoracic portion through the diaphragmatic hiatus into the abdomen. It would therefore be possible for considerable shortening to take place as a result of cicatrization, without leading to a hernia of the stomach into the thorax.

Heterotopic gastric mucosa. Islands of heterotopic gastric mucous membrane may occur in the oesophagus at the level of the cricoid cartilage and also immediately above the cardiac sphincter. As obvious naked-eye structures they are rare; Taylor (1927) found six in a consecutive series of 900 autopsies. Microscopically the structure of the fundal mucosa is faithfully reproduced, the glands possessing both chief and oxyntic cells. As Nicholson (1922) has pointed out, the frequency with which autodigestion

[4] This reference is to an annotation in the *Lancet* on a short unpublished paper read to the Faculty of Radiologists by A. S. Johnstone. The complete paper on oesophageal ulcer by A. S. Johnstone, P. R. Allison, and G. B. Royce, will shortly appear in the *British Journal of Surgery*.

of the surface of these patches is met with *post mortem* supports the view suggested by their structure that they actually secrete gastric juice. It is reasonable to suppose that the juice is continuously secreted in small quantities and collects above the cardiac sphincter, which is normally closed except during the act of swallowing. Though the acid juice is probably in most cases neutralized by saliva which is swallowed frequently in small quantities, it may be present in sufficient excess to lead to digestion of the oesophageal mucous membrane and so give rise to the formation of a chronic peptic ulcer just above the cardiac sphincter. Ectopic gastric mucosa has been discovered in association with chronic oesophageal ulcer in two of the published autopsy reports (Stewart and Hartfall, 1929; Lyall, 1927), but in seven of Lyall's eight specimens none was present. Jackson (1929) saw what he believed were islands of ectopic gastric mucosa in seven of his 21 cases of active chronic oesophageal ulcer examined with the oesophagoscope. The condition is analogous with the chronic peptic ulcers occasionally found in Meckel's diverticulum, which always develop in an islet of ectopic gastric mucosa, as it did in Lyall's (1936) case of oesophageal ulcer, although in Stewart and Hartfall's (1929) case the gastric mucosa was in the upper part of the oesophagus.

Infection and insufficient mastication. The importance of infection as a cause of chronic oesophageal ulcer is strongly emphasized by Jackson (1929), in whose series of 88 cases, open and healed, a focus of infection was found in the tonsils, nasal sinuses, or teeth in 92 per cent., in contrast with only 12 per cent. in a control series of 88 cases of foreign bodies in the air or food passages. More or less dental sepsis was present in all of our patients, except one who was edentulous, but there was no evidence of infection of the tonsils or nasal sinuses. The absence of teeth and the consequent irritation of the oesophageal mucous membrane by unchewed food, especially in poor patients without efficient dentures, is probably of more importance than dental sepsis.

Symptoms

The following description of the symptoms of chronic oesophageal ulcer is founded on our observations during the last eight years on 16 private cases and a rather smaller number seen at Guy's Hospital and the Radcliffe Infirmary. It differs in certain respects from that given by Hurst and Stewart (1929). At that time we had never recognized a case clinically and we based our description on the writings of Jackson, the reports of eight cases collected by Tilestone, and 11 others from the literature.

Pain, which is burning or smarting and often described by the patient as heartburn, is almost invariably present. It is felt whilst actually eating or drinking. At first it occurs only when hard food, such as tough meat, a crust, or piece of apple, is insufficiently chewed, and with chemical and thermal irritants, such as strong alcoholic or very salty drinks, vinegar, hot soup, tea, or coffee, or very cold water or ices. Later it occurs with every meal, but bland fluids, such as milk, can always be drunk without discomfort.

The pain at first lasts for only a few minutes and is at once relieved by alkalies, but later it is more prolonged and less completely relieved. It may amount to no more than discomfort, but it is often so severe that the patient becomes frightened to eat and consequently rapidly loses weight and strength. Pain is also felt an hour or two after meals if the patient bends forward, as in gardening or picking something up from the floor, or if he lifts a heavy weight. He soon learns to avoid such exciting causes; one of our patients had garden tools with very long handles specially made for her so as to avoid bending. In a large proportion of cases the pain returns within a few minutes of lying down at night and also on lying down during the day. In some cases this symptom precedes the pain associated with eating. After a late dinner the pain may waken the patient at 1 or 2 a.m. instead of being felt directly he goes to bed. The intense burning pain behind the sternum is then often accompanied by regurgitation of very acid clear fluid, which he spits from his mouth, in striking contrast with the alkaline waterbrash which frequently accompanies the epigastric or right-sided night pain of duodenal ulcer. Sitting or standing up, arching the back, and stretching the arms upwards may bring relief, which is also brought about by drinking water. Some patients discover for themselves that the night pain can be prevented by keeping the shoulders raised on three or four pillows. The pain is situated in the middle line deeply beneath the lower end of the sternum, corresponding with considerable accuracy to the actual position of the ulcer. Sometimes it passes through to the back between the shoulder-blades, less frequently upwards to the left side of the neck and jaw, and occasionally down the left arm.

The pain felt whilst eating is probably due to the reflex protective spasm of the oesophagus which can be observed radiographically immediately above the ulcer. The approach of a peristaltic wave will cause a rise in the intra-oesophageal pressure and increased tension on the walls of the segment between the circle of contraction caused by the peristaltic wave and the spasm. The pain felt on leaning forward after a meal or lying down is undoubtedly caused by direct irritation of the ulcer by the acid contents of the stomach which regurgitate through the incompetent cardiac sphincter; that caused by swallowed chemical and thermal irritation has probably a similar origin. It is not known, however, whether the nerves exposed in the ulcer can themselves convey painful stimuli or whether some reflex muscular mechanism is involved, as it is in the case of gastric and duodenal ulcers, which are themselves insensitive to all irritants, including hydrochloric acid. A comparison of the symptoms of those cases of chronic peptic ulcer of the oesophagus which are associated with a hernia of part of the fundus of the stomach into the thorax with those in which none is present shows one significant difference. Whilst the substernal pain felt on eating is present in all cases, the pain felt on lying down and on leaning forward an hour or two after meals is observed only in cases associated with a diaphragmatic hernia, as it is in these alone that regurgitation from the stomach into the oesophagus

takes place. It is interesting to note in this connexion that acid regurgitation into the mouth without substernal pain occurs on lying down in some cases of diaphragmatic hernia without oesophageal ulcer. Apart from this an uncomplicated diaphragmatic hernia rarely gives rise to symptoms and is generally an accidental discovery in the course of a radiological examination. In exceptional cases a chronic ulcer develops on the lesser curvature of the stomach at the isthmus between the thoracic and abdominal portions. Two such cases were recorded by Collier, Hurst, and Sheaf (1929), and 16 further cases, including one of his own, were collected by Truesdale (1932).

In the early stages the symptoms generally occur in attacks separated by periods of freedom as with gastric and duodenal ulcer, but sometimes they continue with varying severity for years. In time the patient may learn to avoid certain articles of food which always give rise to pain, to chew thoroughly, to avoid stooping after meals, and to sleep with his shoulders raised. Periods of freedom lasting for years may then follow an attack, but the patient always remains liable to recurrence if he ceases to be careful about his diet. The frequency with which scars of healed oesophageal ulcers are found with the oesophagoscope and *post mortem*, both with and without an active ulcer and with and without a stricture, show how great is the natural tendency towards healing. Occasionally from the onset, but much more frequently after the pain has been present for years, dysphagia develops. The patient notices that insufficiently chewed food appears to stick in the lower substernal region and aggravates the pain. This is followed by noisy gulping. A drink of water often suffices to wash the food into the stomach, or it may be returned into the mouth mixed with saliva, after which the patient finishes his meal. This condition may continue for several years, fluids and thoroughly masticated solid food being swallowed with ease, whilst lumps invariably stick at the lower end of the oesophagus. The dysphagia is at first the result of spasm. Later, if cicatricial stenosis develops, it is more persistent and severe, and leads to regurgitation of food mixed with saliva and sometimes with streaks of blood, which the patient himself clearly distinguishes from vomiting. Of our 16 private patients eight complained of dysphagia, and in four organic stricture was present. The obstruction may finally become complete, when death from inanition occurs unless suitable treatment is instituted.

The obstruction may lead not only to difficulty in the passage of food into the stomach, but also difficulty in belching gas from the stomach into the oesophagus. As reflex excessive salivation may occur with consequent aërophagy, the stomach becomes distended with gas which cannot escape, the condition called *aérogastrie bloqué* (Ramond, Popovici, Dimitresco, and Dany, 1933; Hurst, 1938) being thus produced. The substernal pain caused by the oesophageal ulcer is then accompanied by a still more distressing feeling of distension in the epigastrium, which the patient vainly attempts to relieve by belching, though this results only in its aggravation by further swallowing of air. Failure to recognize the true nature of the condition may have

a deplorable effect upon the patient's nervous system, as in the following case.

Chronic oesophageal ulcer; 'aérogastrie bloqué'. A man of 78 years had suffered from 'gas pains' since 1926. In 1929 and again in December 1931 he had had a small haematemesis; on both occasions he was X-rayed but nothing beyond an excess of gas in his stomach was discovered. Early in 1932 he recognized that there was an obstruction at the entrance into his stomach, as the passage seemed to 'shut up' in a painful spasm whenever food reached it, this being followed by regurgitation of the food with excess of mucus. An X-ray examination again showed no abnormality, except that the left half of the diaphragm was elevated above the right owing to the presence of an enormous gas bubble in the stomach (Plate 3, Fig. 6*a*), as a result of which he complained of very painful flatulence with complete inability to relieve himself by belching. He was regarded as hysterical and was treated by various forms of psychotherapy on the Continent, in America, and in England, but without success. His condition became progressively worse, and when first seen by us in January 1932 he was in a deplorable state of nervousness and was terrified at the mere idea of eating. When a meal was brought into his room, his face became anxious and his hands shook. Several minutes elapsed before he could persuade himself to lift his fork in his trembling hands to his lips; he masticated much longer than was necessary in order to put off the moment of swallowing as long as possible, at the same time shaking his head. He had lost much weight and strength and was extremely depressed.

As it seemed impossible that such severe dysphagia could be purely nervous in origin, especially in view of the history of haematemesis, a further radiological examination was made, and Dr. P. J. Briggs succeeded in demonstrating the presence of a deep chronic ulcer in the extreme lower end of the oesophagus (Plate 3, Fig. 6*b*). Endoscopic examination by Mr. Gill-Carey showed the presence of well-marked oesophagitis, but a persistent spasm prevented the ulcer itself from being seen. A large quantity of occult blood was constantly present in the stools. The *aérogastrie bloqué* was clearly due to the oesophageal spasm caused by the ulcer interfering with the escape of swallowed air upwards, just as it interfered with the passage of food downwards.

The patient was given citrated milk and atropine, and rapidly lost his pain and dysphagia. He soon became comparatively happy, but the physical signs of fear which occurred when food was brought into his room persisted in a lesser degree after the disappearance of the associated emotion, presumably as a result of a conditioned reflex. The ulcer became much smaller, but after many weeks it had not healed, apparently owing to the development of a cicatricial stricture, and eventually a gastrostomy was performed. This resulted in complete healing of the ulcer with disappearance of the occult blood, but at the same time the stricture became still more severe (Plate 3, Fig. 6*c*). This could probably have been overcome by gradual dilatation, but the patient developed an attack of acute mania which proved rapidly fatal.

Occult blood was present in the stools of all of our patients. Haematemesis occurred in three and melaena in one of them. It was rare in Jackson's (1929) series. There was a history of haemorrhage in four out of Lyall's (1936) eight fatal cases, in two of which it was the cause of death. Sudden fatal haemorrhage may follow ulceration of a large vessel, generally the

aorta. Haemorrhage is generally preceded by a long history of pain. Severe anaemia may follow a large haemorrhage or repeated small ones. The constant oozing may be sufficient to cause a moderate degree of anaemia in the absence of any obvious haemorrhage, but in some cases the anaemia is partly nutritional and a result of the restricted diet chosen by or ordered for the patient.

Friedenwald, Feldman, and Zinn (1929) were the first to visualize the crater of an oesophageal ulcer with X-rays, though the accompanying spasm had been observed by Barclay in 1915 and in several of Jackson's cases. It was demonstrated by Dr. P. J. Briggs in 10 of our New Lodge Clinic cases and by Dr. D. T. Barnes and Dr. F. H. Kemp in the cases seen in Oxford (Plates 3 and 4, Figs. 6, 7, 8, and 9). An X-ray examination during the swallowing of a barium emulsion generally shows no abnormality, though the emulsion may be held up by spasm at the lower end of the oesophagus. This accounts for the failure to discover the ulcer during life in any of the eight cases recorded by Lyall (1936). The oesophagus may be slightly dilated, but there is never anything approaching the characteristic mega-oesophagus caused by achalasia of the cardia. When a semi-solid opaque meal is swallowed, or a solid meal is taken at the same time as some opaque emulsion, or when the opaque emulsion is swallowed whilst the patient is lying down, a characteristic picture is obtained. Sometimes it is necessary to raise the foot of the couch or to compress the abdomen. The characteristic picture consists of a narrowing caused by spasm near the lower end of the oesophagus; below this is the ulcer niche, which is generally central, but may be on either side, and below this again is the relaxed cardiac sphincter, in which two or three longitudinal folds can often be recognized, passing to the stomach (Plates 3 and 4, Figs. 6 and 7). In cases associated with a short oesophagus part of the stomach is seen to be above the diaphragm and separated from the rest of it by a comparatively narrow neck (Plate 4, Figs. 8 and 9). The radiographs may then be extremely difficult to interpret owing to the fact that the size of the thoracic portion of the stomach varies greatly under different conditions. In the erect position the mixture of food and gastric juice collects in the dependent part of the stomach and drags some of the thoracic portion into the abdomen. The thoracic portion may then be stretched to such an extent that it assumes the form of a tube little, if any, wider than the oesophagus. The opaque fluid passes rapidly through it and may collect entirely below the diaphragm, so that the existence of a gastric hernia is likely to be missed in a routine screen examination. On lying prone the drag on the thoracic portion ceases and more of the fundus and body of the stomach passes through the much dilated oesophageal hiatus into the thorax. On compressing the abdomen or tilting the table so that the feet are higher than the head, the part of the stomach within the thorax becomes still larger at the expense of that within the abdomen.

It is often advisable to confirm the diagnosis by oesophagoscopy, though the ulcer itself cannot always be reached owing to the spasm just proximal

to it. If there is any doubt about the nature of the ulcer, a fragment of the edge should be removed for microscopical examination. According to Jackson (1929), the characteristic features of the oesophagoscopic appearance of a chronic peptic ulcer are the flatness of the lesion, absence of surrounding infiltration, except in the later stages when the edges are slightly raised and sometimes slightly undermined, and the absence of the exuberant fungations always seen in carcinoma. The ulcer is generally surrounded by a hyperaemic zone and its surface is covered with yellowish exudate: when the latter is wiped away a bleeding granular surface is seen.

Perforation into the pleura, pericardium, or mediastinum is the chief cause of death apart from haemorrhage. We have seen one case in which subacute perforation into the mediastinum probably occurred, but complete recovery followed treatment with large doses of morphia.

It has been suggested that a chronic oesophageal ulcer may undergo malignant degeneration, but we have not found any record of a case in which there was conclusive evidence that this had occurred. In his very extensive experience of oesophageal diseases Jackson met with only a single case in which he believed that a carcinoma had developed in the scar of a healed peptic ulcer and none of malignant degeneration of an active ulcer.

Diagnosis

In most of our cases of chronic oesophageal ulcer, including all of those giving a history of haemorrhage, a clinical diagnosis of gastric ulcer had been made originally, but this had been rejected when X-rays had shown either no abnormality at all or an apparently uncomplicated diaphragmatic hernia with short oesophagus. Similarly, the dyspeptic symptoms in the eight cases recorded by Lyall (1936) were referred to the stomach or duodenum, and in only one, in which at a late stage dysphagia occurred as a result of fibrous stricture, was the possibility of oesophageal disease suspected. The diagnosis is, however, comparatively easy for anyone familiar with the characteristic clinical picture. The radiologist can then be asked to examine the patient with the special technique required for demonstrating small diaphragmatic hernias and oesophageal ulcers.

Just as gastritis may simulate gastric ulcer and duodenal ulcer, so occasionally oesophagitis may give rise to symptoms identical with those of chronic oesophageal ulcer, and the presence of an erosion or acute ulcer may cause manifest as well as occult haemorrhage. In such cases, when the X-rays leave the diagnosis in doubt, oesophagoscopy may settle the question, but it may fail to help, as the spasm, which can always be demonstrated by the X-rays, may prevent access to the ulcer itself.

Achalasia of the cardia should give rise to no confusion, as, although it produces obstruction in the same situation as that associated with an oesophageal ulcer, it never gives rise to substernal pain on eating or on lying down, and any discomfort present is unaffected by avoiding solid food. The

great dilatation of the oesophagus which forms such a characteristic radiographic picture in achalasia of the cardia never occurs with an active oesophageal ulcer, but in one of our cases achalasia of the cardia developed as a late complication after an oesophageal ulcer had healed.

Oesophageal ulcer; recovery; development of achalasia of the cardia four years later. A woman of 56 years, with a 10 years' history of intermittent obstruction at the lower end of the oesophagus, was found by oesophagoscopy to have a small ulcer just above the cardia. The stools contained occult blood, but X-rays failed to reveal any abnormality. Strict dietetic treatment led to the disappearance of the symptoms and of occult blood from the stools, and the oesophagoscope showed that the ulcer had healed. A partial stricture had meanwhile developed and this was successfully treated by dilating with bougies, guided by a string which had previously been swallowed. The patient remained quite well for four years, when she again developed dysphagia, but on this occasion there was no pain and the stools contained no occult blood. X-rays showed the presence of typical achalasia of the cardia, which was rapidly relieved by the use of a mercury bougie. Presumably the scar tissue formed when the peptic ulcer healed had damaged Auerbach's plexus in its neighbourhood and this had led to achalasia of the cardia (Hurst and Rake, 1929).

Carcinoma of the lower end of the oesophagus produces obstructive symptoms from the onset and the pain is rarely as severe as with a simple ulcer, though its localization and radiation are the same. The X-ray appearance is generally quite distinctive, and in doubtful cases oesophagoscopy with biopsy of a fragment obtained from the edge of the ulcer should settle the diagnosis.

The characteristic symptoms sometimes associated with hiatus hernia, a recurrent hernia of the stomach into the thorax through an abnormally patent oesophageal hiatus, the oesophagus being of normal length and free from inflammation or ulceration, resemble those of oesophageal ulcer in so far as attacks of pain occur on lying down and on increasing the intra-abdominal pressure by leaning forward, but the pain has not the burning character of oesophageal ulcer, it never occurs during a meal, it is unaffected by diet, and never brought on by chemical or thermal irritation (von Bergmann, 1932; Hurst, 1934 *a*).

Treatment

The treatment of oesophageal ulcer differs in many respects from that of gastric and duodenal ulcers. The latter are constantly bathed by an acid mixture of gastric juice and food and, when no food is present, by undiluted gastric juice. In contrast with this an oesophageal ulcer comes into contact with acid gastric juice only under certain conditions which allow regurgitation through the incompetent cardiac sphincter with which it is generally associated. Whereas motor activity of the stomach occurs throughout the many hours during which it contains food and to a less extent even when it is empty, the oesophagus is at rest except during deglutition. Consequently a small number of large feeds should replace the small hourly feeds suitable

for gastric and duodenal ulcer. Patients themselves realize that fluid and semi-fluid food can be swallowed without discomfort, whereas solids cause pain, and that anything very hot or very cold should be avoided.

The patient should sit up throughout the day, and at night should have the head of his bed raised by blocks as high as possible so as to prevent regurgitation and stagnation in the lower end of the oesophagus. He is given a pint of milk, which need not be citrated, four times a day. Some of the milk can be replaced by junket, arrowroot, Benger's, Horlick's, custard, or thick white vegetable soup, but the last should not be very hot or salty. About four ounces of water should be drunk five minutes after each feed to wash away any traces of food which might stick to the mucous membrane at the lower end of the oesophagus. An ounce of strained orange or tomato juice should be taken with two of the feeds, and 100 mg. of ascorbic acid, dissolved in milk, should be given daily. Atropine sulphate, gr. 1/100, dissolved in one drachm of water should be given a quarter of an hour before each feed to reduce the tendency to spasm. The dose should be increased by 10 minims every day until an unpleasant degree of dryness of the mouth or paralysis of accommodation occurs; the dose should then be reduced to that of the previous day. A tablespoonful of olive oil should be drunk immediately before each feed; if this is unobtainable one or two teaspoonfuls of cod-liver oil act equally well.

If the X-rays have shown that no diaphragmatic hernia is present and the cardiac sphincter is not incompetent, it can be assumed that hydrochloric acid is being secreted by ectopic gastric mucosa. In these exceptional cases the treatment should be identical with that of gastric and duodenal ulcer, the milk should be citrated, and half a drachm of magnesium trisilicate should be swallowed with a little water in the intervals between the feeds, as it is necessary to keep the acid oesophageal contents as completely neutralized as possible throughout the day.

The strict treatment should be continued until the patient has had no pain or discomfort for at least a fortnight, three consecutive stools have contained no occult blood recognizable by chemical or spectroscopic methods, and the X-rays show no crater. If the ulcer does not heal within a couple of months, or if when first seen an active ulcer is associated with much cicatricial stenosis, specially if secondary stasis in the oesophagus is already present, a gastrostomy should be performed. The ulcer rapidly heals, and when healing is complete, any stenosis which may be present should be treated before allowing the stoma to close. An operation was required in only two of our 16 cases (Hurst, 1934*b*). One of these has already been described (Plate 3, Fig. 6). In the other healing was very slow in spite of the disappearance of pain and dysphagia with medical treatment (Plate 4, Fig. 7). A fortnight after gastrostomy occult blood was no longer present in the stools and the X-rays and oesophagoscope showed no trace of an ulcer. The stoma was allowed to close two months after the operation. There had been no recurrence of symptoms when the patient was last seen a year later.

When the ulcer has healed, the patient should be given a similar post-ulcer régime to that provided for patients with gastric and duodenal ulcer. He should keep the head of his bed raised permanently and should always drink some plain water a quarter of an hour after meals. It is particularly important to eat slowly, chew thoroughly, and to have missing teeth replaced by efficient dentures. Dental sepsis should be completely overcome and infected tonsils should be enucleated. Cicatricial stenosis should not be treated until the ulcer has completely healed. Slight strictures can be quickly overcome by the passage of graduated mercury bougies. Thus in one case dilatation was painlessly effected by the passage in two sittings of mercury bougies from grade 20 to 32. More severe stenosis is treated by the passage of bougies of gradually increasing size, guided through the stricture by a piece of string, previously swallowed, which is threaded through a metal olive at the lower extremity of each bougie. In the later stages the dilatation can be carried out with mercury bougies alone. Finally, the patient should be provided with a mercury bougie which he can pass once a week and subsequently at longer intervals, in order to prevent recurrence of the stricture.

Chronic peptic oesophagitis in the absence of chronic ulcer requires a similar dietetic treatment, but for a much shorter period. The associated spasm can be quickly overcome by the passage of graduated mercury bougies.

Summary

1. Chronic peptic ulcer of the oesophagus is a comparatively common disorder with characteristic symptoms and radiographic signs.

2. It is generally associated with a congenitally short oesophagus and diaphragmatic hernia of a portion of the stomach, a condition which allows the acid contents of the stomach to regurgitate into the oesophagus. The remaining cases are probably caused by the acid secretion of ectopic gastric mucosa in the oesophagus.

3. Chronic oesophageal ulcer responds to appropriate treatment, which differs in certain respects from that of gastric and duodenal ulcer.

4. When the ulcer has healed, special precautions are required in order to prevent a recurrence.

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POSTSCRIPT

On 20.4.42 Dr. E. B. French performed an autopsy at Guy's Hospital on a man of 69 years, who had died two days after an operation for perforated duodenal ulcer. He had been in the hospital three years earlier for retrosternal pain whilst eating and dysphagia. X-rays had shown a stricture at the cardiac end of a short oesophagus, and a diaphragmatic hernia. At the autopsy a chronic peptic ulcer and the scar of a healed ulcer were found at the lower extremity of a short oesophagus, together with a diaphragmatic hernia and a perforated chronic duodenal ulcer. This is the first case in which the association of a chronic peptic ulcer of a short oesophagus with a diaphragmatic hernia has been observed *post mortem*. The association of an active with a healed oesophageal ulcer and with a duodenal ulcer is also of interest.

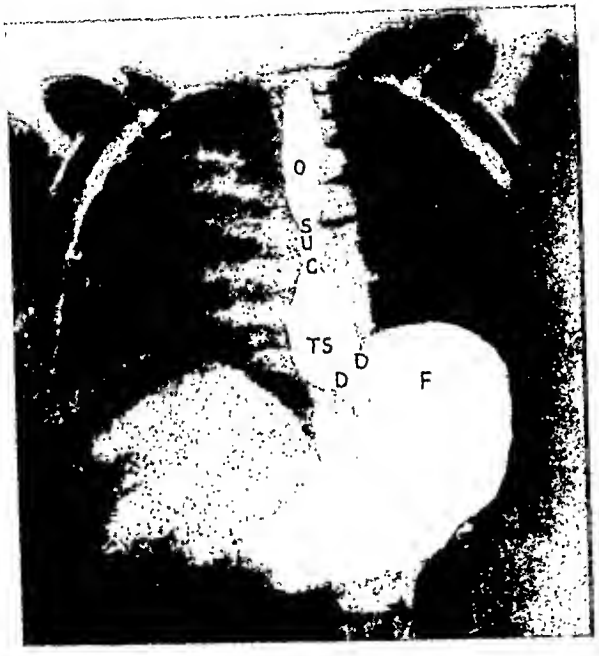
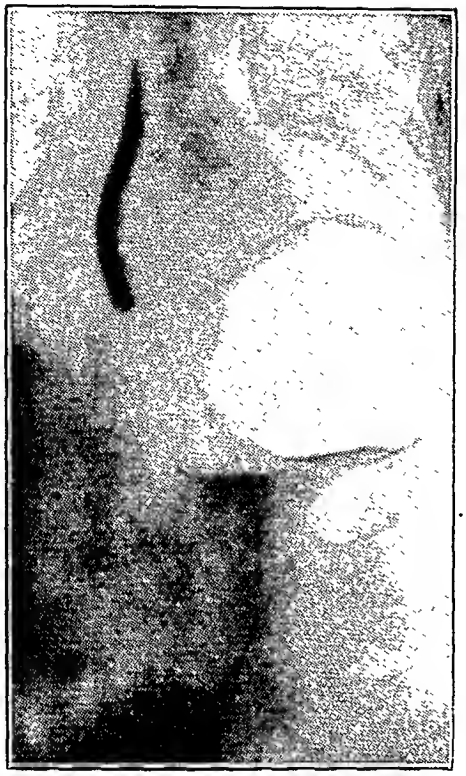


FIG. 3. Radiograph of oesophageal ulcer with congenitally short oesophagus and diaphragmatic hernia in a child of three. O, oesophagus; S, spasm; U, niche of ulcer crater; C, cardiac sphincter; TS, thoracic portion of stomach; DD, level of diaphragm; F, fundus of stomach. (After Haroen and Gerlings, 1934.)

FIG. 4. Photomicrograph of junction between the squamous epithelium of the oesophagus and the columnar epithelium of the stomach in man, × 340 (kindly supplied by Dr. F. C. Lendrum).

FIG. 5. Dissection showing the ∩-shaped strand of oblique muscle which loops over the incisura cardiaca (Dr. F. C. Lendrum).



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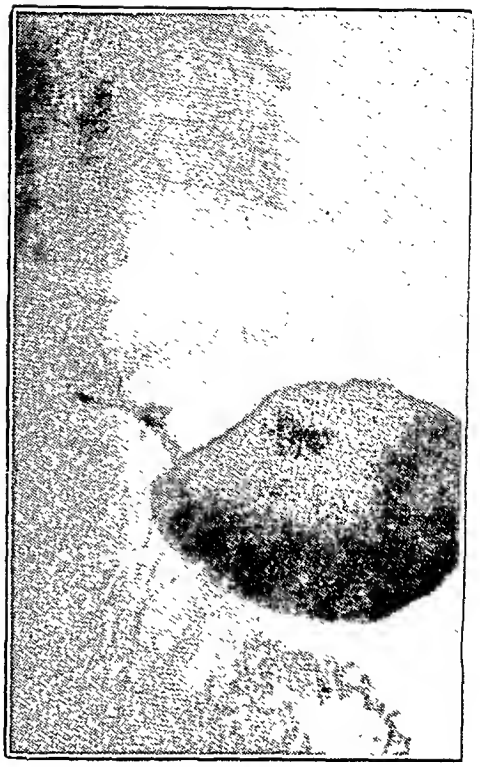

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FIG. 6. (*a*) Aérogastric bloqué secondary to oesophageal ulcer in a man of 78 years. (*b*) Same case as (*a*) showing crater of ulcer. (*c*) Stricture following cicatrization of ulcer shown in (*b*).

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FIBROUS DYSPLASIA OF BONE WITH ENDOCRINE DISORDERS AND CUTANEOUS PIGMENTATION (ALBRIGHT'S DISEASE)[1]

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(From the Nuffield Departments of Surgery and Medicine, Oxford)

With a discussion of the bone changes by A. H. T. ROBB-SMITH

With Plates 5 to 10

Introduction

In 1937 Albright, Butler, Hampton, and Smith described five cases of a curious clinical syndrome characterized by multifocal areas of osteitis fibrosa, patchy cutaneous pigmentation, and in females precocious puberty. In addition they quoted two cases seen by colleagues, and collected 14 similar cases recorded in the literature under various diagnoses. They argued that the association of such diverse pathological manifestations in so many patients indicated a common aetiological factor which, they suggested, might be either a neurological disturbance or a defect in embryological development. Further reports of cases of this condition have since appeared (McCune and Bruch, 1937; Albright, Scoville, and Sulkowitch, 1938; Diez, 1939; Mondor, Ducroquet, Leger, and Laurence, 1939). The recognition of this disease is of importance because it segregates a group of cases until recently confused with other types of bony dystrophy and specially with generalized osteitis fibrosa (von Recklinghausen's disease), with the result that in a considerable proportion of the cases a fruitless exploration of the parathyroids has been done.

In this paper we describe two additional cases and review the literature. In our view the disease consists of a characteristic multifocal fibrous dysplasia of bone in association with endocrine disturbances which vary in type, but have skeletal precocity as a usual feature and may include other less constant features such as sexual precocity, thyroid disorders, and acromegalic changes. Patches of cutaneous pigmentation are also found. It is a disease of childhood and appears to be self-limiting in that the active phase probably terminates simultaneously with the premature fusion of the epiphyses. Although our conception of the condition differs somewhat from that of Albright, we have for convenience alluded to it throughout the text as Albright's disease, since it was he who originally called attention to this particular group of cases. Our two cases are unusual in that they both suffered from severe failure of

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vision and showed acromegalic features, for which they were referred to the Nuffield Department of Surgery, Oxford.. One was a boy aged 10 years with 'osteitis fibrosa', skeletal and sexual precocity, and pigmentation, and the other a girl aged 18 years with 'osteitis fibrosa', skeletal precocity, and pigmentation, but without sexual precocity.

Case Reports

Case 1. M. F., a boy aged 10 years (R.I. 8999).

History. This patient was admitted to the Radcliffe Infirmary in July 1940 on the recommendation of Dr. Wilkie Scott of Nottingham. He was the second of three children, the other children and his parents being healthy. There was no family history of bone disease. He was born at full term, the delivery being uneventful and his birth weight being 6 lb. 4 oz. As an infant his head was thought to be rather large, but was not considered abnormal. His development was normal, his teeth appeared at the usual times, and he began to walk and talk at about 13 months. There was no history of jaundice in infancy. His symptoms started at the age of 3½ years when he began to evert his right foot in walking. A few months later he slipped and fractured his right tibia. Subsequently he had many more pathological fractures, each of which united readily with simple methods of immobilization. These appeared as follows:—

Age in years	Bone affected	Trauma	Period of union	Comment
4	Right tibia	Slight	10 weeks	—
5	Left femur	Trivial	9 weeks	—
8	Right femur	Trod on tennis ball	13 weeks	Subsequently required a stick for walking
9	Right femur	Slight	16 weeks	—
10	Right femur (incomplete fracture)	Slight	12 weeks	Subsequently required crutches

From the age of four years he started to grow faster than normal, and when 6½, as family photographs show (Plate 5, Figs. 6 and 7), he became taller than his brother who was 1½ years older. Thereafter, notwithstanding the shortening of the thighs from deformed femora, he was abnormally tall for his age. From an early age his hands were considered large and his lower jaw prominent. After the age of six years the left side of his face became progressively more prominent. When he was nine years old sexual precocity became manifest. The external genitalia increased in size, and hair appeared in the pubic region. His voice, which had always been gruff, did not alter appreciably. Erections were not observed and his behaviour was normal. With the increasing prominence of the left side of his face, left proptosis appeared, and from the age of eight years the sight in the left eye gradually deteriorated, but the vision of his right eye remained good. He got on well at school. He had never complained of headaches, drowsiness, thirst, or polyuria. Except after the fractures he had had no pains in his bones.

Examination. There was widespread skeletal disorder with bony deformities, excessive growth, and sexual precocity (Plate 5, Fig. 8). His intelligence was normal (I.Q. 113). He was tall for his age, being 5 ft. 4 in. He weighed 8 st. 12 lb. and his general nutritional state was good. His facial appearance suggested a combination of leontiasis ossea and acromegaly. His head was large and massive, measuring 63 cm. in maximum circumference. There

was gross asymmetry of the skull with marked localized bossing of the left fronto-temporal region and the left maxillary region. His left eyeball showed 3 mm. of proptosis and was set at a lower level than its fellow. His lower jaw was prognathous with wide spacing of the teeth, which on biting were set $\frac{1}{4}$ in. in front of the upper teeth. His tongue was large and smooth, while his hands and feet were large and broad. The most pronounced deformities were in the lower limbs where the upper halves of both femora

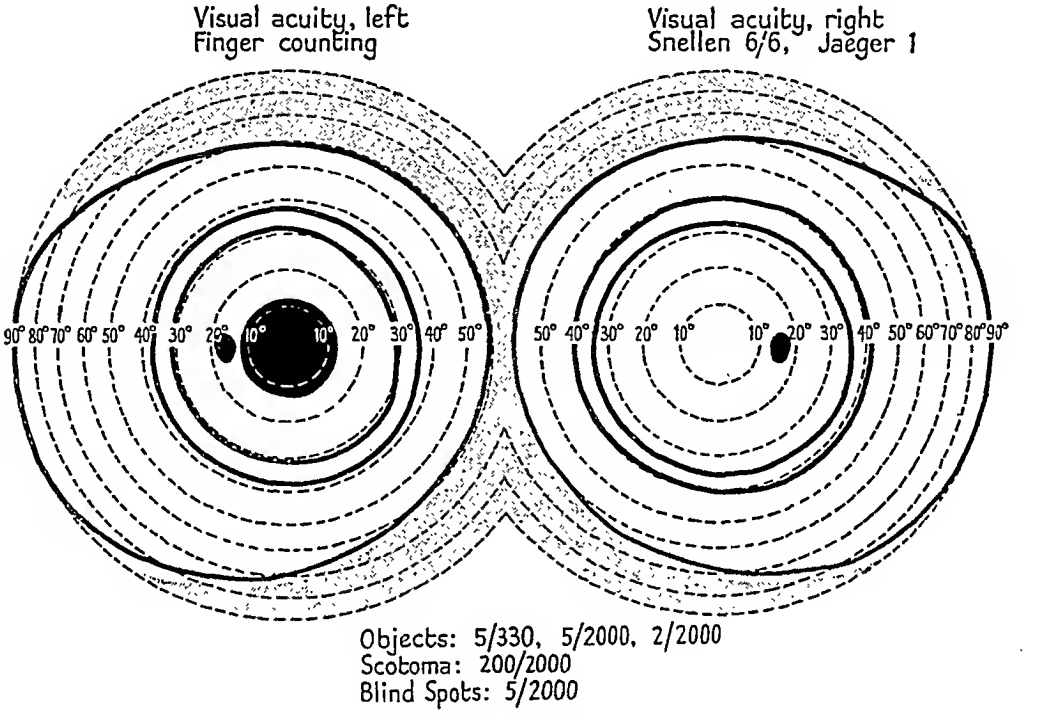

FIG. 1. Case 1. Visual fields

were bowed forwards and outwards, producing bilateral coxa vara with a scissor-like gait. The left leg was $\frac{1}{2}$ in. shorter than the right, but the left tibia was 1 in. longer than its fellow. The trochanteric regions and upper parts of both femoral shafts were greatly thickened, but were not tender. The penis and left testicle were of adult size; the right testicle was of normal size for a boy of his age. There was a slight amount of pubic hair stretching 2 in. above the pubes, but no growth of hair on the face or in the axillae. The only other features of note in the patient's external appearance were two small areas of brownish pigmentation, each about an inch in diameter, in the lumbar region. Examination of the heart, lungs, and abdomen did not show any abnormalities. The blood pressure was 130/60, and the thyroid was not enlarged. The blood-count showed 5,000,000 red cells per c.mm., and 88 per cent. of haemoglobin. The urine contained no albumen, Bence Jones protein, or other abnormal constituent. The blood-urea and urea clearance values were normal, and X-ray examination of the kidneys did not show any calculi or calcification. The basal metabolic rate was normal, but the glucose tolerance curve was slightly raised. The Wassermann reaction was negative in blood and cerebrospinal fluid. The right optic disk showed low grade papilloedema, while the left disk showed moderate optic

atrophy without swelling. The visual acuity in the right eye was 6/6 and J. 1, but in the left eye it was reduced to finger counting. The peripheral visual fields were full, but on the left side there was a central scotoma (Fig. 1). The pupils were equal with normal reactions to light and convergence. There was no weakness or ataxia of the limbs and no impairment of sensibility. Lumbar puncture showed a resting pressure of 220 mm. of cerebrospinal fluid, and unilateral compression of the internal jugular veins produced on the right side a normal rise, but on the left side no rise of pressure. The cerebrospinal fluid was normal (protein 44 mg. per 100 c.c., cells 1).

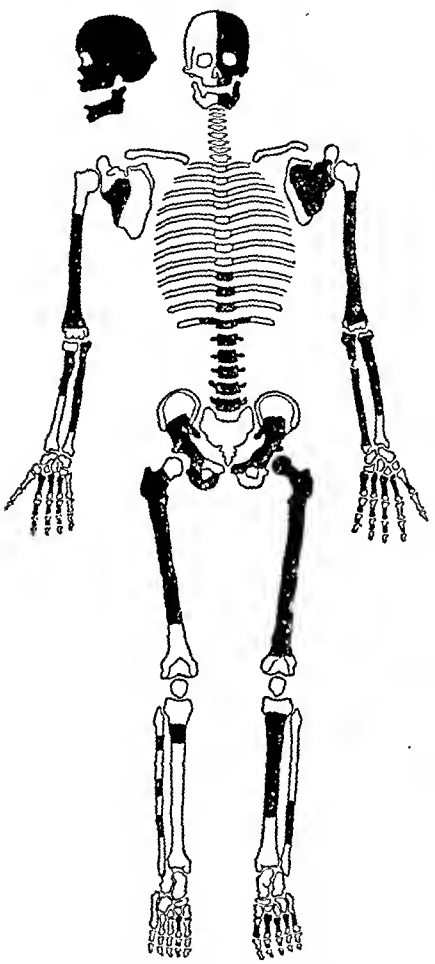

FIG. 2. Case 1. Distribution of bony lesions at age of 10 years

Because of the sexual precocity the daily output of 'androgenic hormones' (17-ketosteroids) in the urine was estimated colorimetrically on two successive days. The technique was that of Callow, Callow, and Emmens (1938) and all the technical precautions advised by these authors were taken. The daily outputs of 6·8 and 6·0 mg. were regarded as normal and not indicative of any adrenal overactivity (Crooke and Callow, 1939).

The appearances seen on X-ray examination of the skeleton suggested multiple areas of 'osteitis fibrosa' with normal bone intervening. The distribution of these areas is outlined in Fig. 2. Although most of the bones were affected, the changes were most pronounced in the skull and both femora (Plate 6, Figs. 10, 11, and 12). In the skull the changes were almost confined to the left side. The base of the skull was distorted by great ill-defined masses of dense bone in the left frontal, sphenoidal, ethmoidal, and superior maxillary regions, surrounding the left orbit and obscuring the sella turcica and the left nasal fossa with its accessory sinuses, except the maxillary sinus. The left optic foramen could not be seen; the right appeared normal. In the occipital region there was extensive deposition of new bone under the pericranium. The left half of the vault of the skull showed a diffuse sclerosis with blurring of its outlines. The ascending ramus of the mandible on the left side was greatly broadened and blurred. Both femora were grossly broadened in the trochanteric region and upper half of the shaft, with marked inward angulation of the subtrochanteric region. The corticalis was thinned and the spongiosa was mottled with myriads of small dense and light shadows, producing a typical appearance which McCune and Bruch (1937) have likened to a column of slowly ascending smoke. The lower part of the femoral shaft on each side was not involved. The appearances in the remaining bones (Plate 6, Fig. 13; Plate 7, Fig. 14) were less marked and

consisted of unifocal or conglomerate areas of homogeneous character usually less dense than the surrounding bone. These areas were occasionally ill-defined, but were usually circumscribed by a linear margin of increased density. A few areas showed increased density. There was no generalized decalcification of the skeleton, although a few bones, especially the phalanges of the hands, showed slight rarefaction. With the single exception of the upper end of the left femur, the epiphyses were not affected, and most of the epiphyseal lines appeared normal. The epiphyseal development, according to the radiological statistics compiled by Paterson (1929), was that of a boy four years older (14 years); four separate epiphyses were present at the lower end of the humerus. A biopsy from the left tibia showed soft vascular bone. Dr. A. H. T. Robb-Smith reported that the microscopic appearances were those of a fibrous dysplasia ('osteitis fibrosa localisata'). Biochemical investigations did not reveal any evidence of hyperparathyroidism. The serum-calcium was low (8·0 mg. per 100 c.c.) although a value of 13 mg. per 100 c.c. had been reported from another hospital. The plasma-phosphate was normal (3·7 mg. per 100 c.c.), but the serum-phosphatase was raised (41 units, Kay). On a constant calcium intake of 172 mg. daily the total calcium excretion averaged 285 mg. per diem in the first three-day period with 32 per cent. in the urine, and 178 mg. in the second three-day period with 57 per cent. in the urine. There was thus no appreciable negative calcium balance. Control calcium balances done by the same method on two cases of proved parathyroid tumour each showed a calcium loss of 250 to 350 mg. daily. The following constituents of the blood were also estimated: plasma-chloride 531 mg. per 100 c.c., plasma-bicarbonate 50 vol. of carbon dioxide per cent., plasma-cholesterol 166 mg. per 100 c.c., and total plasma lipoids 345 mg. per 100 c.c.

Second admission. The patient was readmitted a year later at the age of 11 years for further observation. There had been only slight alteration in his physical condition, and no further fractures had occurred. Although he had fallen over and 'sprained' his left thigh a month earlier, he had continued to use the limb without pain, and X-rays showed no fracture. His parents reported that he was becoming increasingly sensitive about his appearance and did not like being noticed by friends or strangers. He resented not being able to join in the outdoor activities of other boys, and would break out into fits of temper if thwarted. Otherwise his behaviour was normal and his record at school creditable. Re-examination showed that his growth during the year had not been excessive; his height had increased by 1 in. and his weight by $5\frac{1}{2}$ lb. The only striking alterations were that his right thigh had become bowed forwards and outwards almost as much as the left, and his right foot had become rotated inwards. The outer three epiphyses of the lower end of the humerus had fused, indicating a skeletal age of about 15 years (Paterson, 1929). The development of the teeth was in keeping with this skeletal age in that all the permanent teeth had erupted with the exception of the third molars in both jaws and the second molars in the upper jaw. The only other important change was that he had developed a moderate, diffuse, soft enlargement of the thyroid gland. The basal metabolic rate was still normal. The secondary sexual characteristics noted a year earlier had not developed further. There was no change in the visual acuity, visual fields, or fundal abnormalities, nor in the degree of proptosis and displacement of the left eye. Lumbar puncture again showed a resting intracranial pressure varying from 230 to 250 mm. of cerebrospinal fluid, and the Queckenstedt test was again negative on compression of the

left internal jugular vein. The calcium and phosphorus levels in the blood were again found to be normal (serum-calcium 8·8 mg. per 100 c.c., plasma-phosphate 3·3 mg. per 100 c.c.), but the serum-phosphatase was raised to 91 units (Kay). The plasma-cholesterol was 169 mg. per 100 c.c., and the total plasma lipoids were 526 mg. per 100 c.c.

Comment. This case meets the essential requirements of the syndrome under consideration. There was a multifocal fibrous dysplasia of bone occurring in a young boy, in association with endocrine disorders and cutaneous pigmentation. The skeletal disorder differed from that seen in hyperparathyroidism; there was no generalized rarefaction of the skeleton and the metabolism of calcium appeared normal. There was precocious skeletal and sexual development, and in addition there were other features suggesting an endocrine disturbance of multiglandular type. There was, for instance, much in his external appearance to suggest acromegaly, though no other evidence of a pituitary tumour was found. There was also a non-toxic enlargement of the thyroid. Facial asymmetry of the type known as leontiasis ossea was a prominent feature and was associated with marked proptosis and visual deterioration of the left eye. This was apparently due to the great bony overgrowth of the base of the skull compressing the optic nerve and encroaching on the orbit. Similarly the absence of a normal Queckenstedt's response on compression of the left internal jugular vein may have been due to obstruction of the jugular bulb by the same factor; with this may be linked the slight rise of intracranial pressure and the presence of papilloedema in the right eye.

Case 2. J. P., a girl aged 18 years (R.I. 9903).

History. This patient was referred to the Neurosurgical Department of the London Hospital in 1935 by Dr. W. Niccol of Gloucester, and was admitted to the Radcliffe Infirmary for further study in 1940. She was the eldest of four children, the other children and both parents being healthy. She was born uneventfully at full term, her birth weight being 9 lb. There was no history of jaundice in early life. Her development during infancy seemed normal, the milestones of teething, walking, and talking being passed at the usual times. Subsequently as a girl she was always big for her age, but this was not considered unusual as the remaining members of the family were also tall. Her rate of growth, however, was a little faster than that of her brothers and sisters. When five years old she had an attack of anterior poliomyelitis which left her with a little residual weakness of the right leg; the attack was associated with a mild febrile illness, but apparently not with any intracranial manifestations. Symptoms referable to her present condition appeared in 1931 when at the age of 9 years she complained of blurring of vision in her right eye. At a school clinic pallor of the right optic disk was noted, but her visual acuity was found to be 6/6 in each eye. Subsequently vision deteriorated very slowly in both eyes. In her 11th year she sustained a pathological fracture of the right femur, which united readily after immobilization for seven weeks. In November 1934, when nearly 13 years old, she read 6/36 with her right eye and 6/24 with her left eye. Her mother noticed that her face was becoming broader. Apart from an attack of deep-seated headache in 1933 she had been quite free from pain.

Examination. On admission to the London Hospital at the age of 13 years she was an intelligent, well-nourished girl, rather big for her age, and without obvious deformities of her limbs (height 5 ft. 7½ in., weight 8 st. 12 lb.). The base of her nose was broadened and her eyeballs were more widely separated than normal (interpupillary distance 72 mm.). There was slight facial asymmetry, the right pupil being 4 mm. farther from the middle line than

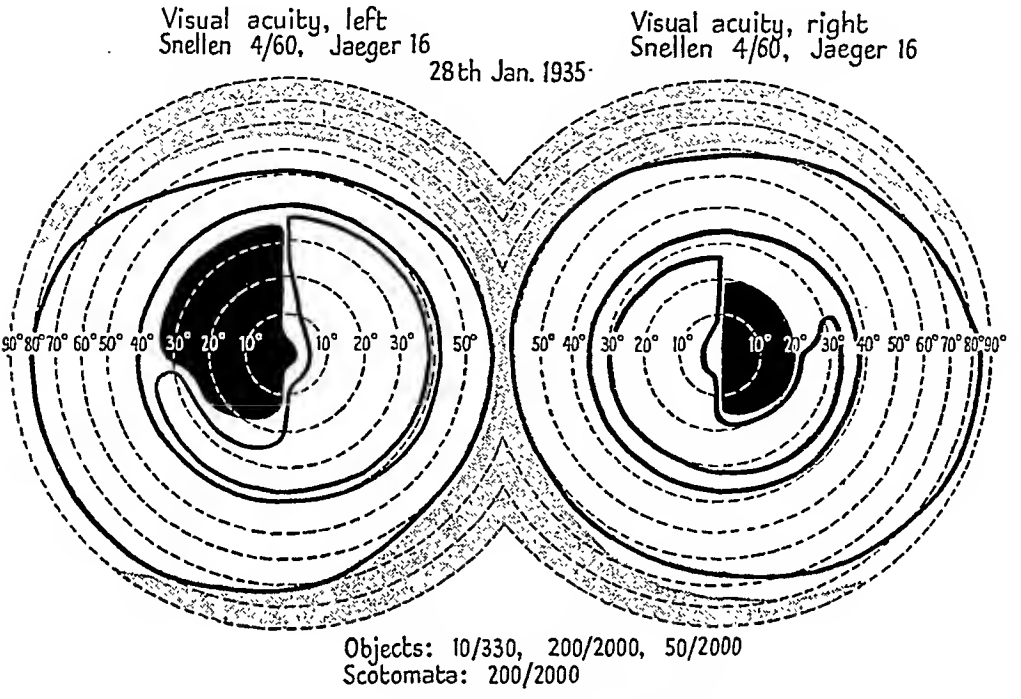

FIG. 3. Case 2. Visual fields at age of 13 years

the left, and there was slight right proptosis. The right frontal and malar regions and the right parietal eminence were more prominent than the left. Her upper teeth were widely spaced, and, on biting, the upper and lower teeth met edge to edge. Her tongue was large but not wrinkled, and her hands and feet were so large that she had had to have her shoes specially made for her. These features, together with the prognathism, suggested a slight degree of acromegaly. The thyroid gland showed slight diffuse enlargement. The menses had not yet appeared, but there was considerable mammary development and slight development of pubic and axillary hair. There was also a small area of cutaneous pigmentation in the lumbar region. Fluid intake and output were normal. The glucose tolerance was normal, although a previous report had suggested the possibility of a diabetic curve. The serum-calcium was 12·5 mg. per 100 c.c. and the plasma-phosphorus 2·9 mg. per 100 c.c. Neurological examination revealed relative anosmia in the right nostril with normal smell perception on the left side. The fundi showed bilateral primary optic atrophy and the visual acuity was reduced to 4/60 and J. 16 in each eye. The peripheral visual fields were full, but the central fields showed large bitemporal hemianopic scotomata (Fig. 3). The pupillary reflexes to light were depressed in keeping with the degree of visual deterioration. The only other abnormal neurological signs elicited were in

the right lower limb where there was slight muscular wasting and weakness of flaccid type, the result of her old attack of poliomyelitis.

X-ray examination demonstrated extensive bony changes similar to those seen in the previous case. The skull showed marked diffuse bony overgrowth of the base, particularly involving the sphenoid bone, right petrous temporal bone, and the bones of the roof and right lateral wall of the nose. The bony overgrowth of the base of the skull was of such a degree as to produce a large hemispherical bony swelling in front of the sella turcica. The outlines of the sella turcica could be only vaguely discerned, but were not enlarged. The right frontal sinus was occluded by the bony overgrowth, but the left frontal and both maxillary sinuses were well delineated. The right half of the vault was thickened and its outlines blurred. In the occipital region there was marked subpericranial deposition of new bone. Examination of several long bones showed that the bony changes were not confined to the skull. The upper third of the right femur showed gross mottling of the spongiosa with expansion of the corticalis on the outer side. Similar but less marked changes were detected in parts of the right tibia, right humerus, right ilium, and in some of the metacarpal bones of the right hand. X-ray examination of some other long bones taken on the same film with a normal control of the same age showed no evidence of generalized osteoporosis. There was thus no evidence of hyperparathyroidism, and consequently a diagnosis of 'focal osteitis fibrosa' was made. The epiphyses were not affected by fibrocystic change. The epiphyses of the lower end of the humerus had united with the shaft, but those of the upper end of the humerus as well as the tibial and femoral epiphyses were still open. According to the statistics of Paterson (1929) these observations would place her skeletal age at between 15 and 18 years, that is from two to five years in advance of her actual age. The development of her teeth was normal for her age, as the permanent second molars had erupted in the upper jaw, but not in the lower jaw.

Because of the visual deterioration Mr. Cairns decided to explore the region of the optic chiasma by a right subfrontal approach. The pericranium was thickened and vascular, as in acromegaly. The outer surface of the skull showed numerous vascular grooves. In places the outer table projected beyond the normal contour of the skull and there it was bluish in colour. The bone was spongy and vascular, and cut easily even where it was thickened. The corticalis was in places very thin, and the thickness of the skull varied considerably, being up to 1·3 cm. at the posterior limit of the exploration just behind the coronal suture. Stripping of the dura from the anterior part of the roof of the orbit exposed a prominent bony projection with numerous bleeding points on its surface. Behind this there was another and larger projection which could not be surmounted, even after the dura had been opened. The inner surface of the dura over the bony mass was quite smooth. To expose the right optic nerve and chiasma it would have been necessary to remove both bony masses together with the rest of the orbital roof, and as this would have entailed considerable blood-loss the operation was abandoned without the optic nerves being seen. Fragments of bone were taken for biopsy.

Pathological Report. Professor H. M. Turnbull has reported on these specimens (London Hospital, S.D. 270/35) as follows:

'Two fragments, pieces (1) and (2), said to have come from the greater wing of the right sphenoid and one fragment, piece (3), from the right frontal bone were decalcified for nine days in 3 per cent. formic acid in

4 per cent. saline formaldehyde and embedded in celloidin. Similar pieces were reserved for decalcification in Müller's fluid, but were not required, because the formic acid preparations showed osteoid zones clearly (Plate 8, Fig. 20). Sections were stained by Ehrlich's haematoxylin with eosin, by Weigert's iron-haematoxylin with van Gieson's mixture, and by Schmorl's thionin phosphotungstic-acid method for cell spaces, canaliculi, and fibrillae.

'*Greater wing of sphenoid, Piece* (1). The fragment is 5 mm. at its deepest. One surface is ragged. The bone beneath, for a depth varying from $\frac{1}{2}$ to 2 mm., contains large medullary spaces filled with slightly fatty, haemopoietic marrow (Plate 8, Fig. 18). A trabecula occupying a small part of this surface contains in one place numerous oblique Sharpey fibres, and probably, therefore, lay close beneath the outer table. The remainder of this trabecula and the trabeculae bounding the haemopoietic medullary spaces are of perfect lamellar bone. On their margins the only sign of past absorption is one short row of empty Howship's lacunae covered with a layer of slender osteoblasts, whilst the only signs of active deposition and absorption are respectively a very few short and shallow osteoid seams and one group of osteoclasts in lacunae. Among these haemopoietic medullary spaces is one space filled with cellular fibrous marrow. On the margins of the bone bounding it are two groups of osteoclasts in deep lacunae, and many shallow empty lacunae covered with a layer of sparse slender osteoblasts. The remainder of the bone, with the exception of a strip of inner table, consists of fibrous marrow in the meshes of a net of irregularly shaped, narrow trabeculae, which consist of woven bone, or such bone deposited upon eroded remnants of lamellar bone (Plate 8, Fig. 18). The fibrous marrow extends into large medullary spaces in the remnant of compact, lamellar inner table, reducing it in most of its extent to a very shallow strip. The fibrous marrow contains engorged capillaries. It is free from inflammatory infiltration. Upon the trabeculae throughout the area of fibrosis are many scattered osteoclasts in lacunae, and several osteoid seams upon which the osteoblasts are usually more numerous and larger than when at rest. The osteoid seams are not abnormally deep.

'*Piece* (2). This fragment is a demilune of 10 × 4 mm. (Plate 8, Fig. 19). The convex surface appears to have been broken off, the straight has been evenly sheared through. In and below the centre of the convex surface large medullary spaces are filled with haemopoietic marrow in slight excess of fatty marrow. One space is prolonged as a narrow process to within a short distance of the flat surface. Close to this a narrow space passes up through the flat surface. The trabeculae bounding these spaces are short and consist of lamellar bone. Their margins are smooth, covered with resting osteoblasts and free from osteoclasts, except in the lower part of one space, where there is a single osteoclast in a lacuna and a few short osteoid seams covered with closely-packed large osteoblasts. This area of bone with spaces containing haemopoietic marrow occupies a third of the section. In the remaining two-thirds a few relatively small medullary spaces, filled with fibrous marrow, pass through or lie immediately beneath the convex surface on one side. A less densely fibrous space contains some haemopoietic cells, and lies immediately below the marrow-filled space which was stated above to have in its lower part osteoid seams and an osteoclast. A considerable distance beneath this, part of another fibrous space passes through the flat surface of the section (Plate 8, Fig. 19). On the bony margins of these small fibrous medullary spaces there are a few areas of active deposition and osteoclastic absorption; in one section one small space is almost completely lined with

osteoclasts in lacunae. The rest of these two-thirds of the section consists of compact lamellar bone, traversed by Haversian canals.

'*Right frontal bone, Piece* (3). The fragment is 7 mm. deep. The outer surface is indicated by numerous oblique Sharpey fibres. The outer 4 mm. are abnormally porous. A chain of considerably widened Haversian canals immediately beneath the surface is followed by numerous medullary spaces of considerable size, directed in the main parallel to the surface. Many, both in the outer and deeper part of this zone, contain adipose partly haemopoietic marrow, but several of them contain areas of fibrous marrow at one extremity or upon parts of their periphery. The remaining spaces are filled with fibrous marrow. The fibrous spaces contrast with the adipose-haemopoietic spaces by having on their margins much more numerous and deeper osteoid seams and a considerable number of osteoclasts in lacunae. The bone in this outer 4 mm. is lamellar. In the inner 3 mm. the remains of an inner table (1 mm. at its deepest) lies beneath a small-meshed net of narrow trabeculae enclosing fibrous marrow (Plate 8, Fig. 20). The fibrous marrow is denser and more cellular than in all except one of the fibrous spaces in the outer 4 mm. Some of the trabeculae consist partly or entirely of woven bone. The remnant of inner table consists of compact lamellar bone, containing one, and sometimes two, dark lines of interrupted growth (Plate 8, Fig. 20). In this inner 3 mm., as is well shown in the figure, active deposition is conspicuous, numerous osteoblasts lying upon osteoid seams which are abnormally deep, the depth frequently being exaggerated by oblique section. Excessive active absorption is shown by a few large groups of osteoclasts and by scattered single osteoclasts in Howship's lacunae.

'*Conclusion.* Two of the three pieces contain typical areas of osteitis fibrosa and the third (sphenoid, piece (2)) contains a little of it. In Paget's osteitis deformans there may be areas indistinguishable from osteitis fibrosa. In my experience other parts of the bone or other bones have then shown the abundant mosaic of small systems which is characteristic of osteitis deformans. The scanty amount of bone examined here makes exclusion of osteitis deformans difficult, and it can be said only that the characteristic of the condition is nowhere present. The section of the frontal bone suggests general osteitis fibrosa, because it is porotic throughout, although in many medullary spaces there is no fibrosis or only small focal areas of fibrosis. In the two sections of the greater wing of the sphenoid, however, there is no evidence of osteoporosis in the parts free from diploe and osteitis fibrosa; the second piece, indeed, consists almost entirely of compacta and diploe. I consider, therefore, that the condition is *focal osteitis fibrosa*. The osteitis fibrosa appears to be extending, as is shown by the partial fibrosis of spaces containing adipose-haemopoietic marrow and the variation in density of the fibrosis in the frontal bone, and by the small fibrotic spaces in the sphenoid, piece (2). The confinement of abnormally deep osteoid seams to areas of exceptionally active osteoblastic activity, shows that the osteitis fibrosa is not complicated by rickets.

'I am indebted to Mr. John King for the sections and photomicrographs.'

Subsequent Course. After operation her vision deteriorated a little further, but from the age of 15 years onwards it remained stationary. Her menses appeared at the age of 13½ years, shortly after operation. They were irregular until the age of 16, after which the menstrual flow recurred every four weeks and lasted five days. When she was 16 years old her walking became difficult, and X-ray examination at the Gloucestershire Royal Infirmary disclosed

a spontaneous and painless fracture of the neck of the right femur. She was given a walking caliper splint, and firm bony union was reported six months later. Her right thigh, however, had become bowed outwards, but she was able to walk without difficulty. There never had been any pain in her bones.

Second Examination. In the Radcliffe Infirmary at the age of 18 years her height was 5 ft. 11½ in., a gain of 4 in. in the previous five and a half years. Her weight was 10 st. 3 lb., an increase of 1 st. 5 lb. Her general

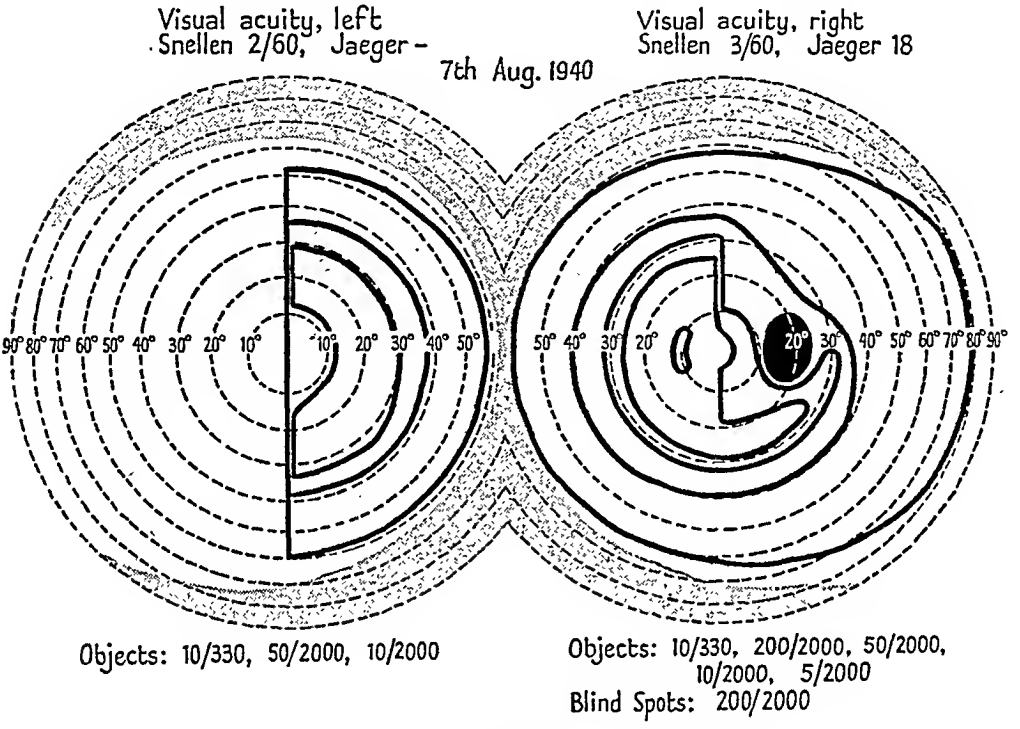

FIG. 4. Case 2. Visual fields at age of 18 years

nutritional state was good (Plate 5, Fig. 9) and her intelligence normal. Photographs show that the facial asymmetry was but little more evident then than it had been five and a half years before. The hypertelorism had increased slightly, the interpupillary distance being 80 mm., but the right pupil was still only 4 mm. farther from the midline than its fellow. The acromegalic features noted earlier had not increased. The external genitalia were well developed, with normal axillary and pubic hair and prominent mammary development. The thyroid gland was still slightly enlarged and contained an adenoma about 3 cm. diameter in its left lobe. The basal metabolic rate was —2 per cent. There was also a moderate degree of coxa vara on the right side. The patch of pigmentation in the lumbar region was unchanged. No abnormality was found on examination of the heart, lungs, or abdomen. The blood-pressure was 140/70. The blood-count showed 4,400,000 red cells per c.mm. and a haemoglobin of 90 per cent. Glucose tolerance was again normal. The urine contained no abnormal constituents, the blood-urea was 28 mg. per 100 c.c. and the urea clearance 140 per cent. of normal. An X-ray of the kidneys did not show any calcification. The Wassermann reaction was negative in blood and cerebrospinal fluid. Neurological examination showed that her impairment of smell was unchanged.

The visual acuity was also little changed, being 3/60 in the right eye and 2/60 in the left eye. The visual fields, however, showed a complete temporal field defect on the left side and an upper quadrantic field defect on the right side (Fig. 4). Lumbar puncture revealed a resting pressure of 120 mm. of cerebrospinal fluid with normal rise and fall on compression of each jugular vein. The cerebrospinal fluid was normal (protein 20 mg. per 100 c.c., cells 1).

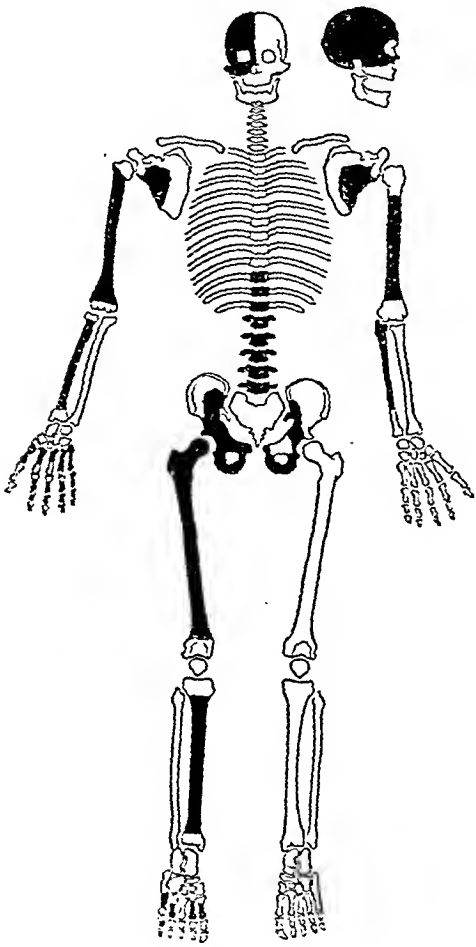

FIG. 5. Case 2. Distribution of bony lesions at age of 18 years

Further X-ray examination showed in places accentuation of the focal bony changes noted five and a half years earlier, but no new foci (Fig. 5). The condition in the base of the skull (Plate 7, Fig. 15) had altered but little in the intervening years. In the right femur (Plate 7, Fig. 16) the process had spread from the neck into the head which had united with the rest of the bone. The neck of the right femur showed marked downward angulation, the result of her painless fracture. The disease was also more extensive in the right humerus, where there was localized broadening of the shaft just above its centre. The other foci in the long bones were also a little more definite (Plate 7, Fig. 17), but no new foci seemed to have appeared in the previous five and a half years. The epiphyses at the ends of the long bones had all united with the shafts, indicating a skeletal age of 20 years or more (Paterson, 1929), but union of the epiphyses of the iliac crests was not complete. There was a full set of permanent teeth in both jaws.

The serum-calcium was 12·6 mg. per 100 c.c., the plasma-phosphate 2·6 mg. per 100 c.c., the serum-phosphatase 30 units (Kay), and the plasma-cholesterol 92 mg. per 100 c.c. On a constant calcium intake of 172 mg. daily, the total calcium excretion averaged 290 mg. per diem in the first three-day period, with 14 per cent. in the urine, and 141 mg. in the second three-day period, with 17 per cent. in the urine. There was thus no appreciable negative calcium balance and so no evidence of hyperparathyroidism. Six months later the blood calcium and phosphorus levels were again estimated and found to be normal (serum-calcium 10 mg. per 100 c.c., plasma-phosphate 3·75 mg. per 100 c.c.) and the serum-phosphatase was raised to 60 units (Kay).

Comment. This case resembles the first one in that a characteristic fibrous dysplasia of bone was associated with clear signs of endocrine disorder and cutaneous pigmentation. The bony dystrophy differed from that seen in hyperparathyroidism in that there was no generalized rarefaction of the

skeleton and the metabolism of calcium was normal. Although there was no sexual precocity, there were signs of general skeletal precocity and features suggestive of acromegaly. There was also thyroid enlargement. It is because of this association of the characteristic bony dystrophy with marked endocrine disturbance and cutaneous pigmentation that we consider this case to be an example of Albright's disease. Like the first patient this girl had defective vision and unilateral ocular proptosis, due apparently to bony overgrowth of the base of the skull, but whereas in Case 1 there was a central scotoma, which is the usual sequel to compression of the optic nerve by overgrowth of bone, in this case there was bitemporal hemianopia with bilateral central scotamata, a type of visual disturbance which implicates the optic chiasma as well as the optic nerves. Chiasmal compression from bony overgrowth must be rare, though when such overgrowth extends backwards and upwards from the optic groove it could act in the same way as a suprasellar tumour. It was considered unlikely that there was a pituitary adenoma causing the chiasmal compression in this case, because although there were some features of acromegaly the picture was not complete and there was no true gigantism; moreover, the sella turcica although largely obscured did not seem to be enlarged. There was no elevation of intracranial pressure and no evidence of compression of the jugular bulbs, such as had been found in Case 1. This case is also of interest in that it indicates that the disease is a self-limiting one. The patient was examined carefully first at the age of 13 years and finally at the age of 18 years. During the intervening period there was only slight change in the bones as judged by X-rays and photographic records of her facial deformity. No fresh foci seem to have appeared, although there had been some extension of the original foci, particularly in the head and neck of the right femur and in the right humerus. Her visual disturbance, too, had become stationary, and her relative anosmia did not seem to have progressed. Moreover, her physical development was now more in keeping with her age; whereas at 13 years she had been an abnormally overgrown girl with precocious development of her skeleton, at 18 years she was normal in height for her age, and her development harmonized with that of the rest of the family. These limitations in the course of the disease coincided with and may be the result of the early closure of her epiphyses.

Discussion

In their original paper Albright, Butler, Hampton, and Smith (1937) defined the cardinal features of the syndrome as '(*a*) bone lesions which have a marked tendency to be unilateral and show osteitis fibrosa on histological examination, (*b*) brown non-elevated pigmented areas of skin which tend to be on the same side as the bone lesions, and (*c*) an endocrine dysfunction which in females is associated with precocious puberty'. They stressed that the bony disorder was not associated with hyperparathyroidism, and so named it osteitis fibrosa disseminata to distinguish it from the so-called generalized (von Recklinghausen's) form of osteitis fibrosa which is associated

with hyperparathyroidism. Our two cases present so many points of similarity to the cases described by Albright and others that there can be little doubt they are examples of the same disease. Both showed similar multiple areas of fibrous dysplasia of bone, both had evidence of endocrine disorder and cutaneous pigmentation, and in neither was there evidence of hyperparathyroidism. They differed from the previously recognized cases in that the female case was not sexually precocious whereas the male case was. They also presented features suggestive of acromegaly and disturbances of vision which have not hitherto been considered as manifestations of this peculiar disease.

In the present paper we attempt to review the various features of the condition, to assess their relative importance, and to determine the relation of this disease to others which seem to be closely allied to it. Our analysis is based on 27 cases, comprising our own two cases and 25 reasonably certain ones collected from the literature. In the selection of these cases difficulty was experienced, for many examples were found in which the clinical picture was incomplete or varied in some way from the original description, and it was not clear whether these should be regarded as examples of Albright's disease. Thus, our female case does not present all the features as originally described by Albright because there was no sexual precocity, but all the other requisite features were present and it seems clear that she was suffering from the same disease. In our view the conception of the syndrome as described by Albright is too rigid, for it excludes cases such as this, which appear on all other grounds to be examples of essentially the same disease process. By making such a rigid definition Albright has been compelled to make separate qualifications for the two sexes whereas, as will be shown later, our broader conception can be made to include both sexes without special qualification for either. However, the 25 cases which we have chosen from the literature for analysis were selected because the clinical descriptions were adequate to show that they met Albright's minimum requirements for the condition he described. They have been published under a variety of diagnoses and the details are summarized in Table I. We have not included all the cases which have been claimed as examples of this disease, but only those in which the published details are sufficient for establishing the diagnosis. Thus, no case published before the last decade has been included, for until the work of Aub (1928) and Hunter and Turnbull (1931) on hyperparathyroidism adequate studies of calcium metabolism were not made in cases of osteitis fibrosa.

General Features. Sixteen cases occurred in female and twelve in male subjects. There is no evidence that the disease is hereditary, in no case were other members of the family affected, and in the one woman (Case 17 in Table I) who had children the disease was not transmitted to the offspring. Albright's disease comes on during childhood and its active phase seems to terminate when adult life is reached. Its onset is insidious. Usually symptoms referable to the bony lesions, such as pathological fractures or skeletal

deformities, are the first to be noted, as shown in Case 1 where they appeared at 3½ years. They may be apparent as early as the first and second years and are almost always present by the tenth year. Occasionally in female cases irregular menstrual bleeding is the presenting symptom, but although it has twice been noted in the first year of life (Cases 17 and 18 in Table I) its onset has usually been delayed until after the appearance of bony symptoms. Pigmentation has never drawn attention to the onset of the disease. Our second case is unusual in that visual deterioration was the initial symptom, but, as later considerations will show, this symptom was really secondary to involvement of the skull by bony overgrowth. Support for the suggestion, first put forward by Diez (1939), that the disease is self-limiting, is furnished by the case histories of the four patients (Cases 3, 9, 17, and 26 in Table I) who were more than 30 years of age. In all of them the condition had been more or less stationary for years, although one (Case 26) had continued to have fractures. Observations in our second case suggest that this quiescent phase is slowly reached when the epiphyses unite with the shafts. On the other hand some activity of the disease, as judged by extension of the bony lesions or by the development of pigmentation or endocrine disturbances, has been recorded during childhood in almost all the published cases. Most of them have come under observation at a stage when symptoms and signs were already well advanced, but in four cases (Cases 11, 20, 21, and 24 in Table I), followed from infancy because of icterus gravis neonatorum, the early stages of the bony lesions and the appearance of cutaneous pigmentation were both observed, and in the three female cases the onset of precocious puberty as well. The active phase of the disease does not lead to a fatal termination, and the only deaths recorded in this condition (Case 8 in Table I; Coleman, 1938) have been from intercurrent causes, but it tends to leave the patient with skeletal deformities which sometimes cripple his activities. It is often difficult to give a prognosis for a case when first seen in early life because the age of onset of symptoms appears to bear little relation to the future severity of the condition. Thus, in one case (Case 17 in Table I), although menstruation had appeared in the first year of life, the patient subsequently bore healthy twins and lived an active life.

The Bony Dystrophy. An essential feature of Albright's disease is the presence in the bones of multiple areas of a fibrous dysplasia ('osteitis fibrosa localisata'). The intervening areas of bone show no demonstrable abnormality or generalized decalcification either by X-ray (Case 2) or in biopsy material (Case 16 in Table I). Both membranous bones and cartilaginous bones may be involved, but the lesions in the long bones differ in form from those in the bones of the skull. Multiple areas of fibrous dysplasia start in the marrow spaces and gradually expand. They originate in the diaphysis but not in epiphyses. The original bony architecture is absorbed and circumscribed areas of rarefaction become visible in the X-ray. Fresh fibre bone may be irregularly deposited in these areas. With continued growth the corticalis

TABLE I

Summary of Cases Reported in Literature

Serial number	Authors	Age	Age at onset of: Bony symptoms	Age at onset of: Puberty	Cutaneous pigmentation	Pathological fractures	Extent of bony disease
MALE							
3	Hirsch, 1929; Gutman, Swenson, and Parsons, 1934	37	Infancy	?	Yes	Yes	Bilateral
4	Cohen and Douady, 1936	26	?	?	Yes	No	Bilateral
5	Albright, Butler, Hampton, and Smith, 1937	14	4	12	Yes	Yes	Bilateral
6	Albright, Scoville, and Sulkowitch, 1938	21	4	Normal age	Yes	Yes	Predominantly unilateral
7	Same authors	14	2	12	Yes	Yes	Bilateral
8	Musser and Barnwell, 1938	11	?7	—	Yes	Yes	Bilateral
9	Pagniez, Pliehet, and Fauvet, 1938	36	3	?	Yes	Yes	Unilateral
10	Lange, 1938	16	4	?8	Yes	Yes	Bilateral
11	Braid, 1939	10	2	—	Yes	Yes	Bilateral
12	Stauffer, Arbuckle, and Aegerter, 1941	19	2½	Normal age	Yes	Yes	Bilateral
FEMALE			Menses				
13	Gaupp, 1932	8	2	3	?	Yes	Bilateral
14	Same author	9	2	9	Yes	Yes	Bilateral
15	Goldhamer, 1934	9	3	2	?7	Yes	Yes	Unilateral
16	Albright, Butler, Hampton, and Smith, 1937	23	8	7	12	Yes	Yes	Predominantly unilateral
17	Same authors	39	10	1	?	Yes	Yes	Unilateral
18	Same authors	6	3½	4½ mths.	6 mths.	Yes	Yes	Bilateral
19	Same authors	8	?	3½	Early	Yes	?	Bilateral
20	McCune and Bruch, 1937	11	1	2	4	Yes	Yes	Bilateral
21	Braid, 1939	2½	1½	2½	—	Yes	Yes	Bilateral
22	Diez, 1939	18	5	5	5	Yes	Yes	Bilateral
23	Summerfeldt and Brown, 1939	13	3	3	5	Yes	Yes	Bilateral
24	Same authors	6	2	2	?6	Yes	Yes	Bilateral
25	Mondor, Ducroquet, Leger, and Laurence, 1939	14	7	7	7	Yes	Yes	Unilateral
26	Robson and Todd, 1939	33	6	7	7	Yes	Yes	Predominantly unilateral
27	Shallard, 1940	18	8	10	10	Yes	Yes	Bilateral

Laboratory findings			Report of bone biopsy	Exploration of parathyroids	Remarks
Serum-calcium	Plasma-phosphatase	Calcium-balance			
					MALE
Normal	Increased	?Normal	Osteitis fibrosa	Negative	--
Normal	—	—	Osteitis fibrosa	Negative	History of two *traumatic* fractures of clavicles; had also neurofibromatosis
Normal	Increased	Normal	Osteitis fibrosa	Negative	—
Normal	Increased	Normal	—	Negative	Segmental neurological signs on trunk; slight gynaecomastia; semen specimen normal
Normal	Increased	—	—	Negative	? Slight sexual precocity
Normal	—	—	—	—	Enlarged thyroid with hyperthyroidism; death after thyroid operation; autopsy
Normal	?Normal	Normal	—	—	--
Normal	—	—	—	Negative	Serum-calcium occasionally raised to 12·5 mg. per 100 c.c.
Normal	Increased	Normal	Osteitis fibrosa	—	Had icterus gravis neonatorum
Normal	Increased	Normal	Osteitis fibrosa	Negative	Congenital arteriovenous fistulae of left arm and leg
					FEMALE
Normal	—	—	Osteitis fibrosa	Negative	Calcium excretion in urine normal
Normal	—	Normal	Osteodystrophy	Negative	—
Normal	—	—	Osteitis fibrosa	—	Serum-calcium 12·2 mg. per 100 c.c. on one occasion
Normal	Normal	Normal	Osteitis fibrosa	—	—
Normal	Normal	Normal	Osteitis fibrosa	—	Gave birth to healthy twins at age of 31 years
Normal	Increased	—	Osteitis fibrosa	—	Exploration of adrenals and ovaries negative; mentally retarded
Normal	Normal	—	Osteitis fibrosa	Negative	—
Normal	Increased	Normal	Osteitis fibrosa	Negative	Had icterus gravis neonatorum; later developed nodular goitre with hyperthyroidism
Normal	Increased	—	—	—	Had icterus gravis neonatorum
Normal	Increased	Normal	Osteitis fibrosa	Negative	—
Normal	Increased	Normal	Osteitis fibrosa	Negative	—
Normal	Increased	Normal	Osteitis fibrosa	—	Had icterus gravis neonatorum
Normal	Increased	—	Osteitis fibrosa	—	—
Normal	Normal	Normal	—	Negative	—
Normal	—	—	—	Negative	Had acute anterior poliomyelitis at age of five years

is thinned from within and the bone weakened, and finally the whole shaft may be expanded. In the absence of trauma the progressive lesion is painless. The bony dystrophy manifests itself usually by pathological fractures with resultant skeletal deformities and sometimes by palpable expansion of a bone. The femur is the commonest site for fracture, and pathological fractures of its upper end have been observed in nearly all cases. Such fractures may result from the most trivial forms of violence; they are relatively painless and unite readily. A good example was afforded by our second case in which a painless fracture of the neck of the right femur occurred without antecedent violence and united soundly within six months, with no more immobilization than that provided by a walking caliper splint. Skeletal deformities are apt to follow union of these pathological fractures and tend to become more disabling as further fractures occur. Coxa vara is the commonest deformity, but others such as genu valgum and kyphoscoliosis are also frequent. Diez (1939) believes that these deformities are always secondary to fractures, but that sometimes the fracture passes unnoticed. In our view the deformities may also be produced by slow bending of softened bones without actual fracture. Thus a marked increase in the deformity of the right thigh was observed in our first case during a period free from fracture, but although fracture and deformity may call attention to the bony lesion, the great majority of the scattered foci of fibrous dysplasia remain symptom-free and are discovered only by a routine radiological examination of the skeleton. If no fractures have occurred the existence of a bony lesion may remain unsuspected unless revealed accidentally by X-ray.

The radiological characteristics are well illustrated by our two cases, although in Case 1 the lesions were more extensive than usual. An analysis of 15 cases in which the distribution of the bony lesions was adequately described (Table II) indicates that any bone in the body may be involved. The femora are apparently invariably attacked, one or both being involved in all the published cases; they are also affected more severely than other bones. Although the head retains its shape, the upper half of the shaft becomes expanded, shortened, and distorted to a remarkable degree. The normal bone pattern is lost. Irregular dense trabeculae may be seen to cross the area in all directions producing an appearance suggestive of a polycystic condition, although no cysts are actually present. This appearance McCune and Bruch (1937) refer to as an 'indescribable confusion of shadows of greater and lesser density, which result in an appearance best likened to a column of slowly ascending smoke'. In the other long bones similar changes may occur, though they are usually less marked and deformities are less frequent than with the femur. Areas of localized rarefaction are found which if large enough may expand the bone and thin the cortex. The same irregular trabeculation and polycystic appearance is seen. Occasionally patches of increased density occur, but areas of rarefaction are commoner. The epiphyses usually escape even though the entire shaft is involved, but once union has occurred they may be attacked by extension from the shaft. This seems to

have happened to one upper femoral epiphysis in our second case, while in Case 1 the femoral epiphysis was involved after fusion had begun but before it was complete. Sometimes the bony lesions are confined apparently entirely to one side (Cases 15, 17, and 25 in Table I). There is also a tendency towards a regional distribution of the lesions so that they are grouped in the bones of one limb or segment of one limb. Our cases show evidence of

TABLE II

Distribution of Bony Lesions in Albright's Disease and Polyostotic Fibrous Dysplasia

Bone	Albright's disease (15 cases*)		Polyostotic fibrous dysplasia (36 cases†)	
Femur	15 cases	100 %	36 cases	100 %
Tibia and fibula	14 ,,	93 %	24 ,, (tibia)	66 %
			10 ,, (fibula)	28 %
Pelvis	13 ,,	87 %	15 ,,	42 %
Humerus	12 ,,	80 %	12 ,,	33 %
Radius and ulna	12 ,,	80 %	9 ,, (radius only)	25 %
Foot	12 ,,	80 %	10 ,, (metatarsals)	28 %
			8 ,, (phalanges)	22 %
Vault of skull	11 ,,	73 %		
Base of skull and face	10 ,,	67 %	6 ,,	17 %
Hand	10 ,,	67 %	8 ,, (metatarsals)	22 %
			6 ,, (phalanges)	17 %
Thorax	10 ,,	67 %		
Vertebral column	9 ,,	60 %		
Shoulder girdle	7 ,,	47 %		

* Cases 1 and 2; and Cases 5, 6, 7, 11, 12, 17, 18, 19, 20, 21, 23, 26, and 27 in Table I.

† Cases collected by Uehlinger, 1940.

this, for whenever a digit was involved the corresponding metacarpal or metatarsal bone was also usually simultaneously involved (Figs. 2 and 5).

The changes in the skull differ in form from those in the long bones, although the essential pathological process is probably similar. The patchy areas of rarefaction with pseudocystic appearance, which are seen in the long bones, are rarely encountered in the skull. The commonest change is an involvement of the bones of the face and base of the skull in a sclerotic overgrowth. This change, if present in the bones of the face, is usually unilateral and imparts a gross asymmetry. The eyeball on the affected side tends to proptosis and to lie both farther from the midline and lower down than its fellow. The sclerotic process in the base of the skull may press on cranial nerves, especially the optic nerve, with resultant visual disturbances. In X-rays the sclerotic overgrowth shows as an area of much increased density which frequently obscures the normal landmarks of the base of the skull, including the sella turcica. In the face the same increased density is seen and the bony overgrowth may obliterate the nasal sinuses. This intense sclerosis makes difficult the satisfactory reproduction of X-rays of the skull. The bones of the vault of the skull may also be involved in a patchy and

irregular thickening resembling in X-ray pictures the appearances seen in Paget's osteitis deformans; in many reports it has been described as 'pagetoid'. This thickening is especially marked in the frontal region where it is predominantly unilateral thereby contributing to the facial asymmetry, and in the occipital region where it is most readily detected by X-rays. The thickening affects particularly the outer table of the skull.

No definite abnormality of calcium metabolism has been observed in this condition. The serum-calcium is usually normal although isolated high values have occasionally been recorded (Cases 1 and 2; Cases 10 and 15 in Table I); there is no increased excretion of calcium and no negative calcium balance; the serum inorganic phosphate values are usually within normal limits. In these respects the condition is different from hyperparathyroidism. As in many other bone diseases the serum-phosphatase is usually raised. Affected bone obtained by biopsy has been examined in practically all cases. The affected bone is soft and spongy (as in our cases) and shows a fibrous dysplasia which is generally described as an 'osteitis fibrosa'. Histologically it has points of difference from the osteitis fibrosa seen in hyperparathyroidism. We are indebted to Dr. A. H. T. Robb-Smith, who examined the microscopical preparations in Case 1, for the following section on the histological appearances.

(*a*) *Histological features.* It is most regrettable that the histological study of the only case of this disease (Case 8 in Table I) which came to post mortem was incomplete; our knowledge is to a large extent based on biopsy material and in many cases the morphological analysis has been superficial. All the accounts are agreed that the changes in the bones are essentially a replacement of the fatty or cellular marrow by fibrous tissue with an alteration of the bony architecture, a condition usually described as osteitis fibrosa. However, in the majority of accounts it is not clear whether the histology is identical with, or different from, that observed in hyperparathyroidism which was so well described by Turnbull (Hunter and Turnbull, 1931). Indeed the whole problem of the morphology of the so-called local osteitis fibrosa awaits critical study.

The observations made here are based to a large extent on the tibial biopsy from Case 1 (R.I.S.H. 1111/40) and on a tibial biopsy from another example of the disease from another hospital (R.I.S.H. 1592/40); the latter is a more satisfactory specimen as it is a wedge of bone, whereas that from Case 1 is a trepanned button which has broken, so that it is impossible to follow the transition from cortex to the depth of the biopsy (Plate 9, Figs. 21, 22, and 23).

The periosteum is normal; the corticalis is formed of laminated bone with normal mosaic systems; the lacunae appear a little larger than usual and are occupied by a loose acellular marrow formed of fat cells, reticulin and collagen fibrils, and fibrocytes; this cortical zone is much narrower than that found in the normal tibia, but within itself shows no abnormality. Immediately deep to this, in the zone where the corticalis normally merges with the trabecular bone, is a layer of fibre bone arising from a dense collagenous stroma which extends to the depth of the biopsy. There is a sharp transition from the normal compact laminated bone to the fibre bone, and indeed there is attritive absorption of the corticalis at the junction.

No laminated trabeculae extend down from the corticalis into the fibrous stroma, nor could any surviving laminae from the original trabecular bone be detected. The new bone is formed entirely of fibre bone by apposition, and there is evidence of very active new bone formation as judged by the broad layer of osteoblasts beyond the osteoid zone; nowhere is the osteoid bone excessively thick in comparison with that of healing fractures. The fibre bone trabeculae are short and closely set, and are interwoven one with another to form a close and comparatively even network; none of the newly formed trabeculae shows any lamination. There is only a moderate amount of osteoclastic resorption and no collections of osteoclasts are present. The marrow is fibrotic; the fibres are coarse and closely set and relatively acellular except for areas where new bone is being formed. There are some almost completely acellular hyaline zones in this dense fibrous tissue. The tissue is strikingly avascular and no haemopoietic marrow is present in the biopsy area. There is no formation of cartilage or xanthomatous area in either of the specimens studied.

Professor Turnbull's precise analysis of the histology of the biopsies from Case 2 is in general agreement with this description, although on the whole his specimens showed a less advanced phase in which there was considerable normal lamellar bone and only small areas of fibre (woven) bone. This description also corresponds well with the majority of published accounts of the biopsy findings in cases of Albright's disease, but with the exception of the report by Dr. Sidney Farber on Case 18 (in Table I) the descriptive histology is so poor as to render interpretation difficult. Usually it was reported that the trabecular pattern was normal, but that there was a fibrosis of the marrow spaces (Cases 17 and 18 in Table I). This is an important observation, for it suggests that the primary change is a marrow fibrosis with secondary absorption of the laminated trabeculae and then a new formation of fibre bone. This is reminiscent of the changes that are observed in myelosclerosis, although in that condition the mesenchymal cells show haemopoietic as well as fibrillo-osteoid propensities.

In many of the biopsies in this disease it is reported that the cortical bone has disappeared and the whole thickness of the biopsy is formed of abnormal fibre bone. This is clearly the ultimate phase of the bony dystrophy and was not observed in our two biopsies. In a few cases (Cases 11, 18, and 20 in Table I) islands of cartilage are reported in the biopsy. In all these the specimen was obtained from the site of a previous fracture, and it should be realized that chondral ossification is a normal phase of the healing of a fracture in healthy bone and may also occur in the healing fractures of bony dystrophies. It is not infrequently formed in fractures of hyperparathyroidism and in 'osteitis fibrosa localisata'. This emphasizes the importance of the selection of the site of biopsy in bony dystrophies, for if the specimen is taken from areas in which secondary changes have occurred the histology will be confused and difficult to interpret.

Albright, Butler, Hampton, and Smith (1937) have stressed and others have observed the relative absence of osteoclastic foci in biopsies and have compared it to the appearances of the bones after parathyroidectomy in hyperparathyroidism. This finding is confirmed in our two specimens. If the interpretation suggested here—a primary collagenous osteogenesis of the marrow with attritive osteolysis of the lamellar trabeculae—is accepted, then this finding is only to be expected, and in the recognition of the condition the well-organized fibre bone pattern is more important than the relative paucity of osteoclasts.

A bony dystrophy, apparently morphologically identical with the osseous lesions of Albright's disease as described above has been defined with great clarity by Lichtenstein (1938). He showed that a form of bony dystrophy, which had remained unrecognized in the cases described as localized osteitis fibrosa or its analogues, had a characteristic clinical, skiagraphic, biochemical, and morphological picture. The morphological analysis, which had been suggested by Dr. Jaffe, showed that in this condition the cellular marrow and trabecular bone was replaced by dense relatively avascular fibrous tissue which underwent osseous metaplasia, and although there was atrophy of the cortical bone in contact with the ossifying fibrous tissue, there was no bony absorption as is found in the skeleton in hyperparathyroidism (osteitis fibrosa generalisata of von Recklinghausen), no cystic spaces, and minimal osteoclastic activity. In an endeavour to make this distinction clear and thus diminish the risk of fruitless parathyroid explorations, he suggested that the bony dystrophy be named 'polyostotic fibrous dysplasia', which, if not euphonious, is at least a reasonably accurate morphological description of the condition without making any presumptions as to its pathogenesis; it is certainly much to be preferred to terms related to osteitis fibrosa or fibrocystic disease. Subsequent authors (Horwitz and Cantarow, 1939; Denstad, 1940; Moehlig and Schreiber, 1940; Stauffer, Arbuckle, and Aegerter, 1941) have accepted Lichtenstein's term in descriptions of the condition and upheld his view that it is a disease entity.

It may be useful to describe briefly the distinguishing features of certain bony dystrophies which are liable on clinical and skiagraphic evidence to be confused with polyostotic fibrous dysplasia. On comparing the bone histology in this condition and in hyperparathyroidism it might appear that there is no essential difference between the former and the sclerotic form of osteitis fibrosa generalisata, but in hyperparathyroidism (Plate 9, Fig. 24) there is commonly some survival of the original trabecular bone, a haphazard arrangement of the fibre bone trabeculae, and foci of osteoclasts in the fibrous tissue, whereas none of these features is observed in the bones in polyostotic fibrous dysplasia. Further, in hyperparathyroidism the cortical bone as a result of decalcification is involved in the fibrous replacement, and a striking feature is the central fibrous replacement of the surviving trabeculae. In Paget's disease (osteitis deformans) there is a loss of contrast between the cortical and trabecular bone with the formation of a new pattern of interlacing trabeculae, and there may be a fibrosis of the marrow spaces. However, in Paget's disease, though there may be foci of fibre bone, the majority of the newly formed trabeculae are made up of metapathic lamellar bone with closely set irregular lamellae giving the characteristic mosaic structure. In dyschondroplasia (Ollier's disease) there is no marrow fibrosis or fibrous replacement whatsoever; instead there are islands of cartilage either within the cortical bone or else as isolated zones between surviving trabeculae. There may be irregularity of the trabecular pattern, but the amount of newly formed bone is minimal. In osseous xanthomatosis (Plate 10, Figs. 25 and 26) the essential change is in the marrow spaces which are replaced by an irregular fibrillo-histiocytic proliferation in which xanthoma cells occur. There is no fibre bone formation. The original trabeculae of laminated bone survive to a variable extent showing attritive and osteoclastic absorption, and there may be slight new bone formation, but this is by apposition, and is lamellar not fibre bone.

Snapper and Parisel (1933) and Snapper (1938, Case 1) reported a case which fulfils all the clinical and radiological criteria of Albright's disease,

but which they regarded as an example of xanthomatosis. A biopsy was performed in the region of the trochanter of the right femur which had been the site of a fracture. The histological material was stained with altered blood. Microscopical examination revealed changes which were for the most part those observed in 'osteitis fibrosa', but in one or two zones there were circumscribed collections of xanthoma cells. On the strength of this observation and the finding of a raised blood-cholesterol on a single occasion, the case was regarded as one of xanthomatosis, but the evidence presented is unconvincing. It is well known that in bones which have suffered intramedullary haemorrhage, xanthoma cells are frequent, and the published photomicrograph is much more suggestive of such a lesion than of true osseous xanthomatosis where there is a close inter-relationship between the polymorphic fibrillo-histiocytic matrix and the xanthoma cells. In true examples of osseous xanthomatosis, as Letterer (1939) and others have shown, there may be areas free from xanthoma cells; indeed it has been suggested by some that the xanthomatous element is only an epiphenomenon consequent on degenerative changes. This view cannot be supported, but it is necessary to recognize that in osseous xanthomatosis the morphological change is a mesenchymal proliferation of histiocytic and desmogenic elements with no osteogenic propensities, but presumably associated with some disturbance of lipoid metabolism. The pattern of the fibre is quite different from that in osseous fibrous dysplasia where there is a primary osteogenic determination and any histiocytic proliferation is only reactive. Snapper's (1938) other cases are clearly not examples of polyostotic fibrous dysplasia and the skiagraphic appearances closely resemble those of osseous xanthomatosis as described by Thannhauser (1940) and other authors. Yet in his second case the first two biopsies revealed only an 'osteitis fibrosa', and it was not until a biopsy was taken from the region of the fractured femur that xanthoma cells were found. The descriptive histology is not entirely clear, but it does suggest, and the photomicrographs still more so, that this was an example of true osseous xanthomatosis, for the connective tissue fibres are arranged irregularly without any sign of osteogenesis, but with considerable proliferation of histioid elements. Snapper's remaining cases are clearly examples of true osseous xanthomatosis.

This discussion has attempted to emphasize the difficulties of interpretation of biopsy material in osseous dystrophies, the importance of selection of material from a site which is not undergoing secondary changes, and the necessity for distinguishing between the changes in the original bony architecture and the new bone pattern. It also stresses the importance of considering the character of the fibrous pattern and the cellular proliferation. Analysed in this way the histological appearances in the bones in Albright's disease are identical with those found in polyostotic fibrous dysplasia.

(*b*) *Relationship to other skeletal diseases.* The bony dystrophy in Albright's disease is frequently confused with the generalized (von Recklinghausen's) form of osteitis fibrosa which occurs secondary to hyperparathyroidism. The distinction is most important since the latter is a remediable disease, but confusion should seldom arise if the points of difference are remembered. In Albright's disease there is no generalized decalcification of the skeleton, no persistent rise in serum-calcium or fall in inorganic phosphate, and no negative calcium balance. Gross asymmetry of the face which is common in Albright's disease is unlikely to occur in hyperparathyroidism. Although

the X-ray appearances in the long bones may simulate the lesions of hyperparathyroidism, the polycystic appearances assumed by the femur in Albright's disease are distinctive. Involvement of the skull, when present in Albright's disease, is of a type quite different from that due to hyperparathyroidism; localized areas of dense sclerosis occur in the former, a tendency to generalized rarefaction in the latter. Patients with Albright's disease will usually give a history of skeletal abnormality in childhood; hyperparathyroidism is usually active in adult life. In spite of these differences the two conditions have often been confused in the past so that 15 out of the 27 collected cases have been submitted to a fruitless exploration of the neck. The absence of a parathyroid tumour was also demonstrated in one case of the disease which came to post mortem and also in a second probable case reported by Coleman (1939), but not included in our series. Albright, Butler, Hampton, and Smith (1937) have remarked on the several points of resemblance radiologically and histologically between the bony dystrophy in Albright's disease and the condition of the bones some time after the removal of a parathyroid tumour, for when healing occurs after hyperparathyroidism the generalized decalcification disappears, osteoclastic activity ceases, and the areas of fibrosis become sclerotic, although the cystic areas still retain their outlines. It is very improbable that the bone changes in Albright's disease are the result of a past 'burnt out' hyperparathyroidism for, as has been pointed out by Dr. Robb-Smith, the essential pathological process is different. Moreover, several cases were observed over a long period of their active phase (Cases 11, 18, and 20 in Table I) and in none was evidence of a disturbance of calcium metabolism obtained.

In discussing the pathological features of the bony lesions of Albright's disease, Dr. Robb-Smith has called attention to the apparently identical histological picture seen in a clinical entity recently separated by Lichtenstein (1938) from the general group of so-called 'osteitis fibrosa' and named by him 'polyostotic fibrous dysplasia'. Uehlinger (1940) has collected a number of cases of this condition from the literature and described the clinical picture. According to his analysis the essential features of 'polyostotic fibrous dysplasia' are:

1. A lesion of bone developing in the marrow spaces and consisting essentially of a fibrous dysplasia which leads to expansion and atrophy of the shaft and eccentric pressure atrophy of the cortex.

2. The lesion may involve one, several, or many bones and may be unilateral or bilateral, though not symmetrical; it is never generalized.

3. There is a special predilection for the long bones and the neighbouring shoulder and pelvic girdles. Proximal bones are more extensively affected than distal bones. The frequency of distribution of the lesions is shown in Table II. The femur appears to be invariably involved.

4. The disease affects primarily the diaphysis. Joints and epiphyses remain unaffected except in rare cases when the disorder may spread to the epiphyses after their union with the metaphyses (compare our two cases).

5. The base of the skull often shows an intense sclerosis, and the cranial vault a thickening of the outer table.

6. The serum-calcium and inorganic phosphorus levels are normal, the phosphatase normal or slightly raised.

7. The condition is a disease of childhood and becomes stationary in adult life.

From Uehlinger's full description it is clear that in its clinical behaviour as well as in its histological appearances this condition resembles in all respects the bony lesions of Albright's disease. Lichtenstein himself regarded his 'polyostotic fibrous dysplasia' as identical with Albright's 'osteitis fibrosa disseminata'. Uehlinger also takes this view and points out that the condition has also been described by various authors as 'osteodystrophia (osteitis) fibrosa unilateralis', 'osteitis fibrosa with multiple foci', 'unilateral Recklinghausen's disease', and 'osteofibrosis deformans juvenilis'.

The original cases collected by Lichtenstein as examples of his 'polyostotic fibrous dysplasia' did not show endocrine features or cutaneous pigmentation. It seems that these accompaniments are infrequent in this bony disorder because sexual precocity or manifest endocrine disorder was recorded in only four of the 36 cases of 'polyostotic fibrous dysplasia' collected by Uehlinger. These four cases appear to be examples of the condition which we are describing as Albright's disease. Since the identity of the bone lesions in the two conditions seems established on both clinical and histological grounds, Albright's disease must be regarded as an association of cutaneous pigmentation and endocrine disturbances—of which the most striking is precocious puberty in girls—with a characteristic bony disorder which may occur by itself. This fibrous dysplasia resembles Ollier's dyschrondroplasia (Hunter and Wiles, 1934) in that both diseases are active during childhood, but become quiescent during adult life, and both show the same tendency towards unilateral and regional distribution of the bony lesions. It differs from dyschondroplasia in that it affects membranous bones as well as cartilaginous bones, and therefore cannot be regarded as secondary to some abnormality of cartilage development. Sexual precocity and cutaneous pigmentation have not been reported in association with dyschondroplasia (Albright, Butler, Hampton, and Smith, 1937; McCune and Bruch, 1937). As a rule the radiological appearances are quite distinct, but occasionally dyschondroplasia may show a similar X-ray picture, as in an unusual case described by Dahle (1939). In such cases the differentiation may have to be made by biopsy as the histological appearances of the two conditions are different (see preceding section by Dr. Robb-Smith).

Diez (1939) referred to juvenile Paget's disease in discussing the differential diagnosis of Albright's disease. Although most authorities consider that Paget's osteitis deformans occurs only in middle and later life, Hummel in 1934 described two cases of a multifocal bony dystrophy in boys, which he regarded as juvenile Paget's disease. Both cases showed also marked patchy cutaneous pigmentation, but no evidence of hyperparathyroidism. A bone

biopsy was obtained in one case and was reported as showing the fine mosaic structure considered by Schmorl as characteristic of osteitis deformans, but the published X-rays and photomicrograph are not convincing of this diagnosis. The relationship of these two cases to Albright's disease is uncertain, although Albright, Butler, Hampton, and Smith (1937) and McCune and Bruch (1937) considered them to be examples of their syndrome. Because of this uncertainty we have not included them in our series.

It is possible that some cases reported as leontiasis ossea may have been examples of this same bone disorder, for leontiasis ossea has been a marked feature of our own and several other cases of fibrous dysplasia of bone. It is generally recognized that leontiasis ossea is not a specific disease, but a particular clinical appearance which can result from at least two different pathological processes. Knaggs (1923) in his classical paper on leontiasis ossea showed that many cases were due to 'osteitis fibrosa', but unfortunately his observations and those of most other writers on the subject were based on dry skulls or on cases recorded without reference to the rest of the skeleton.

Endocrine Features. (*a*) *Skeletal precocity.* As already stated it is the association of endocrine features and cutaneous pigmentation with a characteristic fibrous dysplasia of bone which, in our opinion, characterizes Albright's disease. Of these endocrine features precocious skeletal development should be regarded as the most common. It was noted by Albright, but was not given the same prominence as sexual precocity, probably because the latter, when it occurs, is much more striking. But skeletal precocity occurs with greater frequency than sexual precocity and, unlike the latter, is common to both sexes. Hence by focusing attention on the skeletal rather than on the sexual precocity a more uniform clinical picture is obtained in the two sexes. Evidence of skeletal precocity has been found in all the cases in which it has been possible to estimate the epiphyseal age during childhood (Table III). Such evidence is not available in every case reported because some were not observed until adult life and in others the necessary data were not recorded. The skeletal precocity is generalized and not confined to those bones which show radiological evidence of fibrous dysplasia. The precocious development of the epiphyses may be associated in the early stages with rapid growth of the skeleton so that the child is often big for its age. This was noted in both our cases. As epiphyseal union also is accelerated (Case 2; Cases 10, 13, 14, 19, 20, 22, and 25 in Table I) growth ceases prematurely so that the adult patient does not become a giant, and may even be small. The generalized nature of these signs of skeletal precocity and the fact that they are not confined to bones showing radiological evidence of fibrous dysplasia indicates that they cannot be attributed to the irritant effects of the local bone lesion on the nearby epiphysis. They are therefore presumably endocrine in origin. Similar premature union of the epiphyses with early cessation of growth has been observed in cases of precocious puberty from other causes, but in at least three examples of Albright's disease (Case 2; Cases 5 and 7 in Table I)

skeletal precocity occurred in the absence of sexual precocity. The skeletal precocity cannot, therefore, be regarded as merely the result of the sexual precocity. It may be an invariable accompaniment of the 'polyostotic fibrous dysplasia', but evidence on this point is not available, since the skeletal age has not been recorded in children suffering from polyostotic fibrous dysplasia without other endocrine features.

(*b*) *Sexual precocity in female subjects.* This was common to all the cases collected by Albright and has been a prominent feature of most of the

TABLE III

Epiphyseal Ages of Certain Recorded Cases

Case	Sex	Actual age (years)	Epiphyseal age (years)	Sexual precocity
Case 18 in Table I	F	3½	7 to 8	Yes
Case 15 in Table I	F	4	15	Yes
Case 19 in Table I	F	8	over 17*	Yes
Case 13 in Table I	F	8	over 17*	Yes
Case 14 in Table I	F	9	over 17*	Yes
Case 20 in Table I	F	9	18 to 22	Yes
Case 1	M	10	14	Yes
Case 2	F	13	15 to 18	No
Case 5 in Table I	M	14	16 to 17	No
Case 7 in Table I	M	14	17	No
Case 25 in Table I	F	14	over 17*	Yes
Case 10 in Table I	M	14	over 18*	Yes
Case 22 in Table I	F	18	over 20*	Yes

* Estimated from published X-ray photographs in accordance with Paterson's (1929) statistics; remaining figures obtained from published records.

cases published more recently. Our own case is unusual in being sexually normal, although in all other respects she appeared to be suffering from the same disease. In all the remaining cases which we have collected the menses appeared before the tenth year. The age of onset of menstruation and puberty in the individual cases is given in Table I; in the youngest case (Case 18 in Table I) vaginal bleeding appeared first at the age of 4½ months and the secondary sexual characteristics at 6 months. The menses are irregular and scanty at first, but soon afterwards the secondary sexual characteristics begin to appear and the cycle becomes regular. These secondary sexual characteristics are normal in type, remaining essentially feminine and showing no tendency to virile features. Possibly an analogous development takes place in the internal generative organs, as McCune and Bruch (1937) observed an unusually enlarged uterus in their patient when 4½ years old (Case 20 in Table I). The urinary excretion of gonadotrophic and oestrogenic hormones was studied in several cases (Cases 16, 17, 18, 20, 22, 23, 25, and 26 in Table I), but no significant elevation of these substances has been reported. Exploration of the adrenals and ovaries was undertaken in one case (Case 18 in Table I), but no abnormality was found; ovarian tumours have not been palpable in other cases. No information is available about sexual desire in this condition. Pregnancy was observed in one established

Occasional Features. (*a*) *Icterus gravis neonatorum.* This condition has been observed in four cases (Cases 11, 20, 21, and 24 in Table I). The jaundice was of unusual type as bile pigments were absent from the stools. Two cases evidently recovered spontaneously and the other two after a single blood transfusion had been given at the end of the first week to arrest bleeding. Cerebral symptoms indicating an associated nuclear jaundice were apparently not observed. Braid (1939) postulated that this condition was in some way responsible for the later appearance of bony lesions, but it was not observed in most of the collected cases, and we inquired for it specifically in our two patients with negative results.

(*b*) *Neurological symptoms.* Occasionally when there is marked leontiasis ossea neurological symptoms may arise through compression of cranial nerves and other structures by the bony overgrowth, as was seen in our two cases and in Braid's case (Case 11 in Table I). In this way we can explain such symptoms and signs as the visual deterioration, optic atrophy, unilateral ocular proptosis, and defects in the visual fields observed in Cases 1 and 2, and also the compression of the internal jugular bulb in Case 1, the unilateral anosmia in Case 2, and the deafness in Braid's case. A similar mechanism involving the vertebral column probably also explains the alterations in the abdominal and cremasteric reflexes associated with impaired cutaneous sensibility, which Albright, Butler, Hampton, and Smith observed in one of their cases (Case 6 in Table I).

(*c*) *Anterior poliomyelitis.* In two cases (Case 2; Case 27 in Table I) the appearance of symptoms directly referable to the syndrome of Albright's disease was preceded by an attack of what seems to have been acute anterior poliomyelitis. These attacks were associated with a short febrile illness, but not apparently with intracranial symptoms. Both patients were left with slight residual weakness of a limb of the type commonly seen following this disease. The connexion of these attacks with the later development of symptoms of Albright's disease is not known.

Pathogenesis

The aetiological factors causing Albright's disease are not known. Post-mortem examinations have been made in a definite case of the disease and in a possible example not included in Table I because of lack of evidence that either endocrine disturbance or cutaneous pigmentation was present. In Musser and Barnwell's (1938) case (Case 8 in Table I), a boy aged 11 years who died after an operation for hyperthyroidism, no abnormalities were seen in the testes, adrenals, or parathyroids. The thyroid showed a diffuse colloid goitre and the thymus was unusually enlarged. The brain, spinal cord, and pituitary were not examined. In the probable case (Coleman, 1938), a boy aged 13 years who died of acute pancreatitis, no macroscopic abnormality was visible in the brain, testes, prostate, thyroid, adrenal, or pituitary. The parathyroid bodies were not seen. The right kidney was atrophied. An interesting incidental finding was a saccular aneurysm of the ascending aorta.

In the absence of significant post-mortem findings, the cause of this disease must remain a matter for conjecture. It does not appear to be hereditary, and is apparently not due to syphilis. At least two hypotheses have been advanced. Albright, Butler, Hampton, and Smith (1937) argued that the tendency for the bony and cutaneous lesions to be confined to one side suggests an embryological or neurological defect rather than a primary endocrine dysfunction. Later, in support of this argument, Albright, Scoville, and Sulkowitch (1938) instanced a case in which unilateral impairment of motor and sensory functions occurred in the lower thoracic segmental areas on the same side as most of the bony and cutaneous lesions. On the strength of this case they put forward the view that the whole syndrome is due to a disseminated neurological lesion and that the sexual precocity can be ascribed to lesions around the third ventricle. However, the neurological signs which they observed in their case may have been due to compression of nerve roots by the associated involvement of the vertebral column. Braid (1939), impressed by the occurrence of icterus gravis neonatorum in her two cases, felt that hepatic dysfunction was responsible for the later symptoms, but was unable to give a satisfactory explanation of the mechanism. Icterus gravis neonatorum has been recorded in only a few cases, although its frequency seems to indicate more than a chance association.

In considering the pathogenesis of the condition it is necessary to bear in mind the relation between the cases described by Albright and those having the same bony dystrophy, but no endocrine features or cutaneous pigmentation. In our view there is no sharp distinction between these two groups. The bony dystrophy occurring by itself is becoming recognized under the name 'polyostotic fibrous dysplasia' proposed by Lichtenstein (1938). Although none of the cases collected by Lichtenstein was described as having cutaneous pigmentation, yet cases do occur in which cutaneous pigmentation is present, and this alone is apparently sufficient in male subjects for them to be accepted by Albright as examples of his syndrome. Whether polyostotic fibrous dysplasia can occur in association with endocrine features but without cutaneous pigmentation is uncertain, since small patches of pigmentation may easily escape special mention in case reports unless their significance is appreciated. In Mochlig and Schreiber's (1940) case of a boy with polyostotic fibrous dysplasia and gynaecomastia, pigmentation is not recorded.

It seems probable therefore that endocrine disturbance and cutaneous pigmentation occur in association with polyostotic fibrous dysplasia as largely independent variables. Indeed, in our view all gradations will be found from the condition as described by Lichtenstein without endocrine disorder or pigmentation to the extreme case described by Albright, Butler, Hampton, and Smith (1937) of a girl with the same bony disorder, who developed precocious puberty at the age of six months (Case 18 in Table I). If this view should prove to be correct then the distinction between polyostotic fibrous dysplasia on the one hand and Albright's disease on the other

would become arbitrary and merely one of degree. It is possible, of course, that all cases of polyostotic fibrous dysplasia do present minor endocrine features which have hitherto not been noted, and this point must await further investigation, but in the meantime it seems desirable to keep separate as a distinct clinical group those cases having clear endocrine features. It is this group which we consider should be called Albright's disease, regardless of the form which the endocrine abnormalities may take. On this view some male cases which were accepted by Albright because they had the bony lesion and pigmentation, would be ineligible because they lacked manifest endocrine features, but nomenclature is of less importance than is the clear recognition of the relation between these cases of Albright's on the one hand and uncomplicated polyostotic fibrous dysplasia on the other. Though all three features of the disease show considerable variation in their severity, it cannot be assumed that their association is fortuitous. Both cutaneous pigmentation and endocrine disorders occur with such frequency in cases having the bone disorder that it seems safe to conclude that they have a common actiological basis.

From the pathological point of view the bone lesion consists essentially of a disturbed development of the undifferentiated mesenchyme with resultant fibre formation. There is no tendency to neoplastic change and no evidence of inflammation (Lichtenstein, 1938). The histological picture provides no clue to the cause of this dysplasia, but its tendency at times to be unilateral certainly suggests a congenital defect, as does also the association with patchy cutaneous pigmentation. Its focal distribution is not readily explained on a hormonal basis, and, indeed, no known disorder of the endocrine system can produce a comparable bony lesion. If the condition is congenital, then the occasional occurrence of icterus gravis neonatorum and arteriovenous fistulae (Case 13 in Table I) may reasonably be regarded as associated congenital abnormalities. This possibility was recognized by Braid (1939). Probably the endocrine abnormalities also are manifestations of this congenital defect, though their origin is obscure. It is tempting to attribute the skeletal precocity, the not infrequent enlargement of the thyroid with occasional hyperthyroidism, and especially the acromegalic features of our own two cases, to pituitary dysfunction with increased production of gonadotrophic, thyrotrophic, and growth hormones, but this is purely speculative. The precocious puberty cannot be so explained since this is not a recognized result of pituitary dysfunction; it has never been observed to result from pituitary tumours, but it is possibly significant that the sexual precocity observed in Albright's disease is similar in type to that resulting from hypothalamic lesions. Moreover, a number of cases have been recorded in which sexual precocity has resulted from congenital lesions of the hypothalamus (hamartomas and cranio-pharyngiomatous cysts). They have been reviewed recently by Weinberger and Grant (1941). In these cases the lesions were visible macroscopically, but there seems to be no good reason why a smaller congenital lesion in this area should not have as pronounced an effect. Only

by postulating both a congenital bone defect and a congenital hypothalamic defect does it seem possible to provide an explanation of the association of such diverse phenomena in one disease, and the combination is most easily regarded as an error of early embryological development.

Summary

1. Two cases of fibrous dysplasia of bone associated with endocrine disturbances and patchy cutaneous pigmentation are described. They are examples of a disease which was first reported by Albright, Butler, Hampton, and Smith in 1937. Our two cases differ from most previously recorded cases in that sexual precocity was observed in a male patient, but not in a female one, while both cases showed features suggestive of acromegaly and also leontiasis ossea with visual disturbance.

2. These two cases and others recorded in the literature are reviewed, and a broader concept of the disease is advocated. The essential features of the disease are a characteristic multifocal fibrous dysplasia of bone occurring in association with endocrine disorders of variable type. Skeletal precocity is a common feature, but other less constant features such as sexual precocity, thyroid disease, and acromegalic changes may be present and may dominate the clinical picture. Patches of cutaneous pigmentation are usual.

3. The bony dystrophy is identical with a variety of 'localized osteitis fibrosa' which has recently been defined by Lichtenstein (1938) and called polyostotic fibrous dysplasia. It is a distinct entity and can be clearly distinguished from the bony dystrophy of hyperparathyroidism by the absence of generalized osteoporosis, the absence of a demonstrable disturbance of calcium metabolism, and by a characteristic histological picture. It is not associated with parathyroid tumour.

4. The same bony dystrophy can occur without endocrine features or cutaneous pigmentation, but it is the presence of these associated features which distinguishes the disease described by Albright. It is probable that all gradations will be found, from the uncomplicated polyostotic fibrous dysplasia occurring alone, to the fully developed syndrome of Albright's disease.

5. The disease appears in childhood and becomes stationary in adult life. It is not fatal. There is no evidence that it is hereditary. Its pathogenesis is unknown, but it seems probable that it is the result of a congenital disorder of development involving both the bony skeleton and the hypothalamus.

We wish to thank Professor Hugh Cairns for permission to publish these two cases and also for his great assistance in the presentation of this paper. We are also indebted to Professor H. M. Turnbull for the pathological report in Case 2, to Dr. M. H. Jupe and Dr. F. H. Kemp for radiological reports, to Mr. J. R. P. O'Brien for blood analyses, and to Miss A. J. Arnott and Miss M. Hering-Shaw for technical help with the illustrations.

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ADDENDUM

Since the present paper was written Lichtenstein and Jaffe (1942) have reviewed and extended their conception of the disease entity named polyostotic fibrous dysplasia. Their view of the relation between this condition and that which we call Albright's disease is essentially the same as our own. They regard the latter as a severe form of the former, the bony lesions being the same in both.

Reference: Lichtenstein, L., and Jaffe, H. L. (1942) *Arch. Pathol.* **33**, 777.

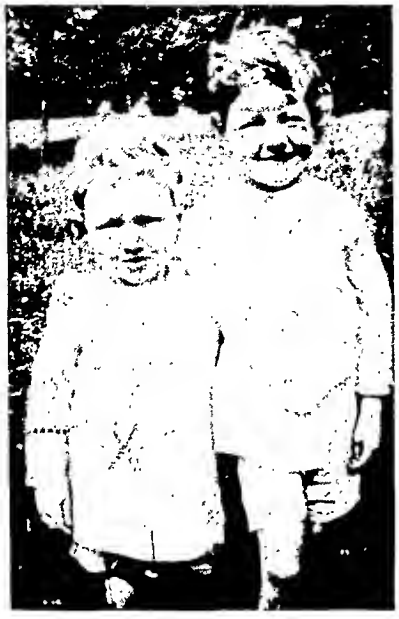

FIG. 6. Case 1 at age of 2½ years with elder brother aged 4 years

FIG. 7. Case 1 at age of 6½ years has now outgrown elder brother aged 8 years on right

FIG. 8. Case 1 at age of 11 years

FIG. 9. Case 2 at age of 18 years

FIG. 10. Case 1. Skull showing appearances of leontiasis ossea

FIG. 11. Case 1. Skull showing appearances of leontiasis ossea

FIG. 12. Case 1. Left femur showing pseudocystic appearances

FIG. 13. Case 1. Left humerus showing pseudocystic appearances

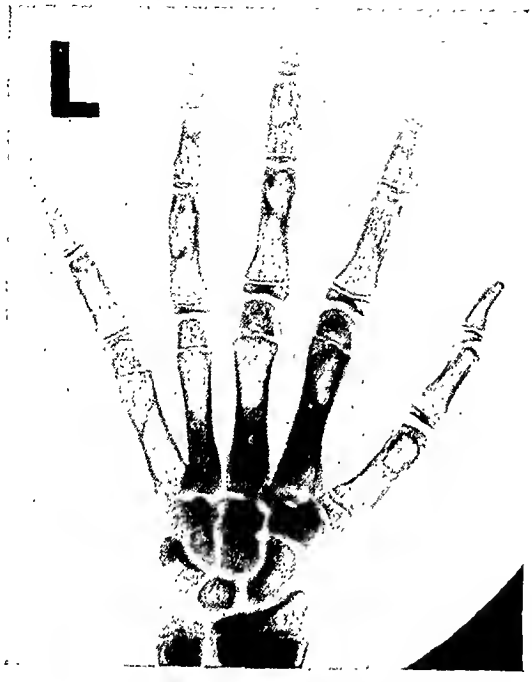

FIG. 14. Case 1. Left hand showing pseudocystic appearances

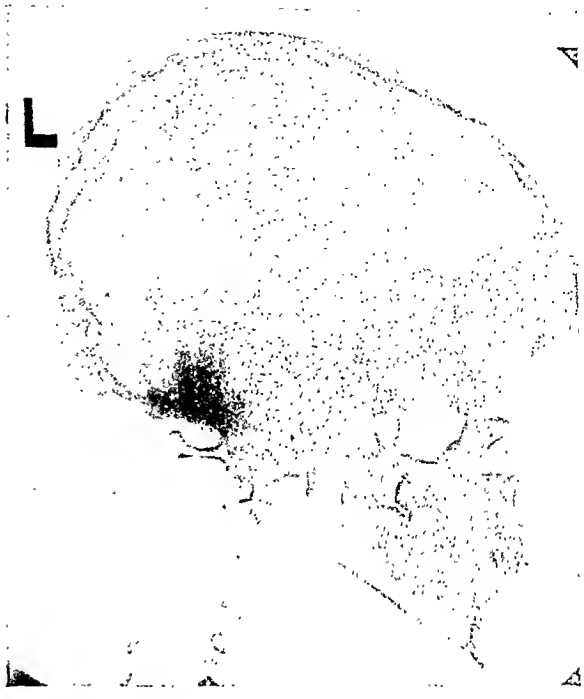

FIG. 15. Case 2. Skull showing appearances of leontiasis ossea, at age of 18 years

FIG. 16. Case 2. Right femur showing pseudocystic appearances, at age of 18 years

FIG. 17. Case 2. Right tibia showing area of sclerosis in upper part and area of rarefaction below this

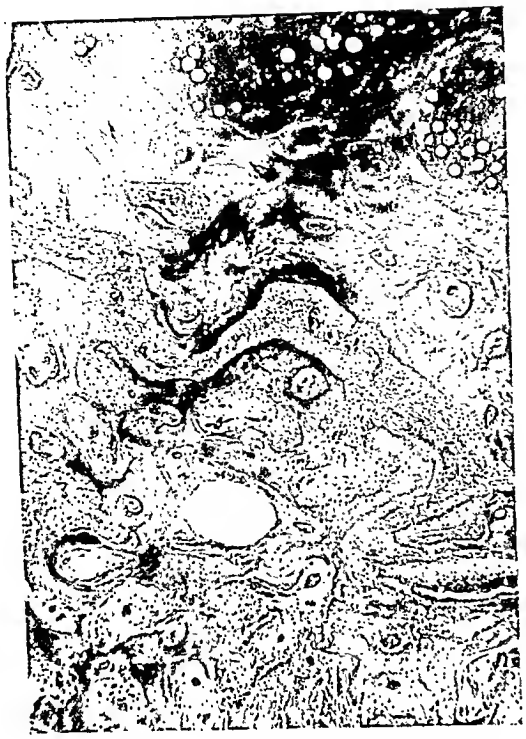

FIG. 18. Case 2. Sphenoid bone, piece (1). (Haematoxylin and eosin, ×26)

FIG. 19. Case 2. Sphenoid bone, piece (2). (Haematoxylin and eosin, ×10). Arrows point to fibrotic spaces

FIG. 20. Case 2. Frontal bone, inner 3·4 mm. (Haematoxylin and eosin, ×26)

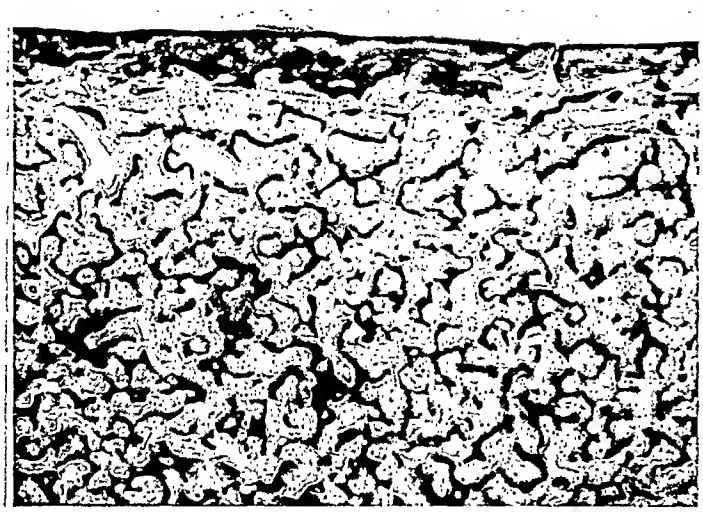

FIG. 21

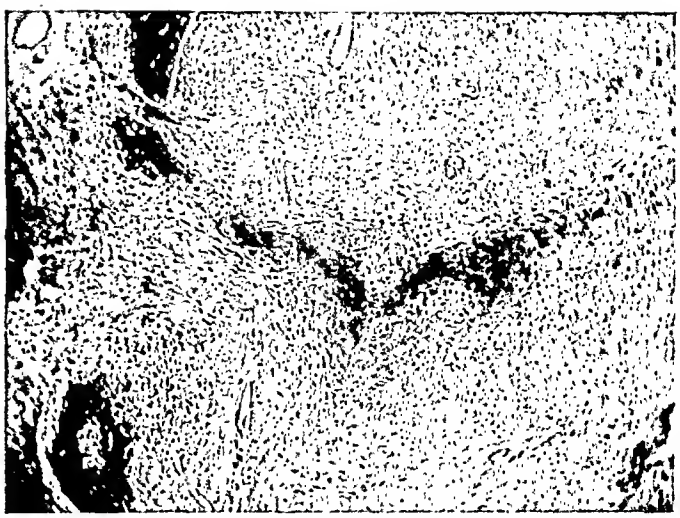

FIG. 22

FIG. 21. Tibia. Polyostotic fibrous dysplasia (R.I.S.H. 1592/38). The photomicrograph shows the thin but normal cortex of lamellar bone and the complete replacement of the medulla by a fibrous marrow in which a close-set pattern of fibre bone trabeculae is arising by metaplasia; none of the original lamellar trabeculae of the cancellous bone has survived (Masson's Trichrome Stain, ×10·7)

FIG. 22. Caso 1. Tibia. Polyostotic fibrous dysplasia (R.I.S.H. 1111/40). The photomicrograph shows the early formation of a fine bone trabecula by a metaplastic change in the fibrils of the fibrous marrow (Masson's Trichrome Stain, ×63)

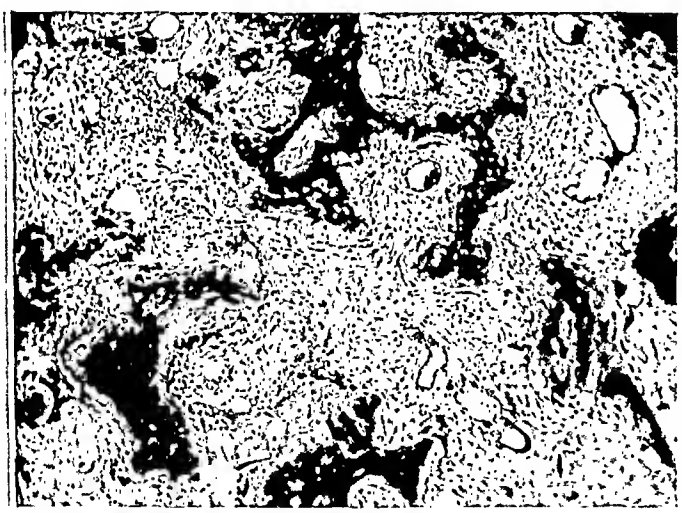

FIG. 23

FIG. 24

FIG. 23. Case 1. Tibia. Polyostotic fibrous dysplasia (R.I.S.H. 1111/40). The photomicrograph shows the close-set fibre bone trabeculae merging imperceptibly with the fibrous stroma. Note the broad osteoid zone and poor calcification (Masson's Trichrome Stain, ×63)

FIG. 24. Tibia. Hyperparathyroidism (R.I.P.M. 281/40). The photomicrograph shows a normal periosteum and replacement of the outer layer of the corticalis by fibrous tissue in which there are bony trabeculae formed by apposition. The outer part of the cancellous portion is largely replaced by fibrous tissue, but isolated trabeculae of lamellar bone survive and the newly formed pattern of fibre trabeculae are in relation to the surviving lamellar bone. Islets of haemopoietic marrow are lying in the fibrous stroma (Masson's Trichrome Stain, ×10·7)

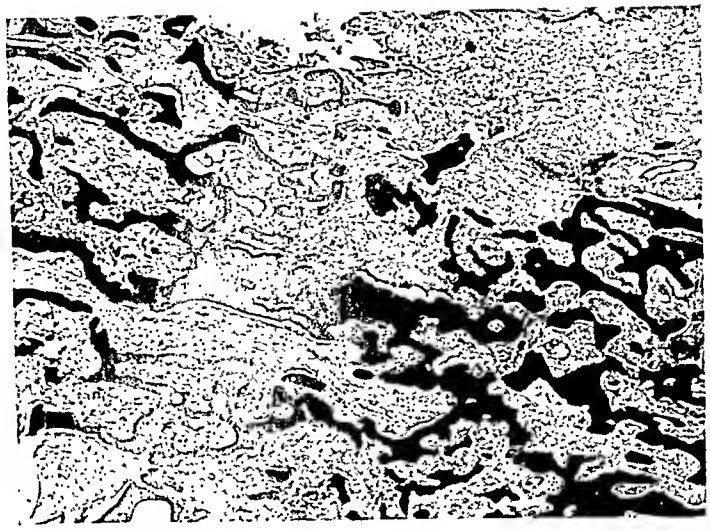

FIG. 25. Tibia. Xanthomatosis (R.I.S.H. 1708/40). The photomicrograph shows attritive absorption of the lamellar bone of the cancellous layer and the fibrillo-histiocytic tissue filling the interstices. There is no new bone formation (Masson's Trichrome Stain, $\times 10.6$)

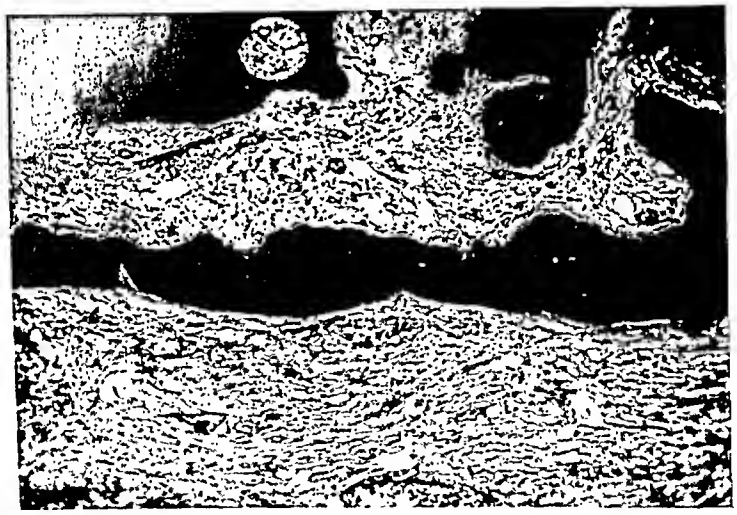

FIG. 26. Tibia. Xanthomatosis (R.I.S.H 1708/40). The photomicrograph shows a trabecula of lamellar bone with some attritive change surrounded by the fibrillo-histiocytic tissue. Above the bony trabecula the tissue is loose in structure with numerous xanthoma cells, below the trabecula it is denser, but the pattern of fibres bears no relation to the bony tissue and is quite different in character from that seen in fibrous dysplasia of bone (Masson's Trichrome Stain, $\times 67$)

616.24–002

PNEUMONIA IN INFANTS, CHILDREN, AND ADULTS[1]

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Introduction

The recognition by Fränkel and by Weichselbaum in 1884–6 of the pneumococcus as the usual cause of pneumonia was followed, about a quarter of a century later, by the separation of the organism into a number of types. More recently, as knowledge concerning the antigenic properties of the constituents of the bacterial cell was elaborated, sera possessing antibodies specific to certain individual types were prepared and administered to patients with lobar pneumonia, and consistently decisive therapeutic results were obtained for the first time. In fact, when chemotherapy was introduced a few years ago, serum treatment had attained great efficiency and was being widely used. Moreover, the interest aroused had stimulated much valuable research, so that methods of diagnosis had become more rapid and accurate, a good deal had been added to the knowledge of the epidemiology of the disease, and concepts built around morbid anatomy had become amplified by observations which more satisfactorily explained the clinical picture in terms of local and general immunity (or lack of them) to invasion by a particular type of pneumococcus or other pathogen.

At first sight it may appear that the success of drug treatment has detracted from the value of these researches and removed them to the academic sphere. The relative simplicity of drug treatment is without question, but the services of the laboratory are essential if serum is to be used. The implicated pneumococcus has to be isolated and identified, and the administration of the homologous serum is a hospital procedure requiring time and experience. Indeed, so far as this country is concerned, it may be accepted that under present conditions serum treatment is likely to be neglected or left to a few enthusiasts, so that little fresh information may be forthcoming about the natural history of pneumococcal pneumonia, and this is to be regretted. A certain proportion of pneumococcal pneumonias fail to react to the appropriate serum, and the same may now be said of some cases treated with sulphapyridine. Information gathered only from painstaking clinical and bacteriological assay will enable us to discover the reasons for failure and to use the resources at hand with maximum benefit. To this end

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the typing of pneumococci associated with the pneumonias is a prime requisite. The following series, collected in an area subjected to heavy air-raids, is presented with the object of showing that, despite certain inadequacies, much useful information can be obtained, and in the hope that work of a similar nature may be undertaken elsewhere.

Clinical Material

The clinical status of the patients was assessed on admission. A blood culture was taken in the majority of cases before treatment was started, being omitted where the condition seemed to be resolving or the patient was afebrile. Laryngeal swabs were taken from infants (0 to 2 years) and generally also from older children. The tongue was depressed by a spatula, and a cotton swab on the end of a bent silver wire introduced behind the epiglottis. When the larynx was touched, gagging was usually followed by cough and the adhesion to the swab of a small amount of mucus from the trachea. Swabs were taken on admission, or on the morning after admission. From adult patients sputum was collected in a sterile container. Administration of sulphapyridine was not witheld until the specimen was procured. The pneumococcus from secretions collected 12 to 24 hours or longer after the first dose could be typed as readily as those from secretions before the drug had been given.

The usual symptomatic treatment such as the use of the oxygen tent was given to patients when necessary, and diet and sedatives followed the hospital practice. The dosage of sulphapyridine given to infants was approximately that advocated by Hartmann, Barnett, Perley, and Ruhoff (1940), 0·2 gm. per kilogram of body weight per diem. The drug was supplied in tablets of 0·125 gm., and it was found most practicable to administer it in this dosage or multiples of it. Accordingly, the dose prescribed was frequently a fraction of a tablet more or less than the body weight assessment. The drug was given four-hourly, and the first dose was double that of subsequent doses. Adults were given 2 gm. as the initial dose and 1 gm. four-hourly thereafter. Children (2 to 12 years) were given half the adult dose. No attempt was made to restrict or standardize the intake of fluids in order to influence the concentration of the drug in the blood and body-fluids. Some patients who appeared to be recovering were not given sulphapyridine on admission. While most of these made satisfactory progress, a certain number did not, and were given the drug for the first time after several days in hospital.

Laboratory investigations. A saline emulsion of the sputum was inoculated intraperitoneally into a mouse. Swabs were stirred in approximately 1 c.c. of nutrient broth. A direct film was made from this mixture and stained by Gram's method. The swab was then plated on a fresh blood plate and ½ to 1 c.c. of the impregnated nutrient broth inoculated intraperitoneally into a white mouse. Before inoculation the broth was incubated for two hours, save in a few cases where the swab was received fresh and was obviously very moist. The fresh blood plate was examined after 24 hours'

incubation and the predominant organisms identified and recorded, particular attention being paid to pneumococci and haemolytic streptococci, on the latter of which a soluble haemolysin test was done. The mice were killed after 48 hours, unless definitely ill, when they were killed after 18 to 24 hours. Only those mice which remained particularly lively were left for 72 hours before being killed. Typing was done by the Neufeld method on the peritoneal fluid of the killed mouse. The peritoneal fluids were stained by Gram's method and plated on to fresh blood, whether pneumococci were found or not. Pneumococci which were not recovered from mouse inoculation, but grew on culture on blood-agar, were emulsified in saline, inoculated into a second white mouse, and typed from this. If they were not recovered from the second mouse, the pneumococci were reported as avirulent to mice. Blood cultures in broth were examined daily, blood plates being inoculated after 24, 48, and 72 hours incubation.

The concentrations of sulphapyridine in the blood were determined by the method of Bratton and Marshall (1939). All the estimations save one were carried out immediately the blood was received. In all cases the amount of the free drug was determined, and where this was low, a further estimation of the total amount of sulphapyridine in the blood was carried out.

One hundred and ninety-one infants, children, and adults were admitted to the hospital from December 1940 to the end of July 1941 with a provisional diagnosis of pneumonia. These were finally placed in the following categories, (1) primary pneumonia, 110 cases, (2) pneumonias secondary to measles or pertussis, 29 cases, (3) other secondary pneumonias, 3 cases. Forty-nine cases remain; 37 of these proved to be bronchitis, alone or associated with some other disease, and 12 were unrelated conditions. The pneumonias in the first two categories are shown in Table I and will be discussed in detail.

TABLE I

Age Groups and Clinical Types of Primary Pneumonias and Pneumonias secondary to Measles and Pertussis

Pneumonia 139	Infants 57	Bronchial 44	Primary 32 (21)		
			Measles 9 (6)		
			Pertussis 3 (2)		
		Lobar 13	Primary 9 (7)		
			Measles 4 (4)		
	Children 38	Bronchial 22	Primary 9 (3)		
			Measles 7 (3)		
			Pertussis 6 (3)		
		Lobar 16	Primary 16 (11)		
	Adults 44	Bronchial 3 (1)			
		Lobar 41 (33)			

The figures in parentheses indicate the number from which pneumococci were isolated.

I. *The Primary Pneumonias in Infants and Children*

The term 'primary pneumonia' is used by some authorities to cover all pneumonias resulting from the inhalation of known or unknown bacteria or viruses, regardless of the anatomical distribution and pathology of the process

in the lung, and to distinguish such pneumonias from those which arise in connexion with antecedent disease. Those who would employ the term in this sense argue that it is frequently difficult to make any clinical distinction between lobar and bronchial pneumonias, especially in infants and young children, and that there is an essential identity between them in that the same organism is capable of producing either variation, not as a matter of chance, but depending upon the cellular resistance in the lung in a given case, or upon the product of that resistance and the humoral antibodies available to meet the action of the invading organism.

While there is much to be said in favour of this conception, we feel that the clinical exercise of deciding whether a pneumonia is of the lobar or bronchial type has a good deal of practical value, and that it may be premature to neglect the differentiation until more information has been acquired about the bacteriology, particularly of the bronchial form of pneumonia. There is the further point that most authors distinguish between the two types of pneumonia in reporting their series, and that comparison with their work is difficult unless this course is followed. Accordingly, we shall use the term 'primary pneumonia' in the present paper to describe those pneumonias, both lobar and bronchial, which have arisen independently of other conditions.

The primary pneumonias numbered 110, of which 66 were lobar and 44 bronchopneumonia. Forty-one of the total were in infants and pneumococci were isolated from 28. Twenty-five were in children and pneumococci were isolated from 14. Forty-four were in adults and pneumococci were isolated from 34. The monthly incidence is shown in Table II.

TABLE II

Monthly Incidence in Primary Pneumonia (all ages)

	Dec.	Jan.	Feb.	Mar.	Apr.	May	June	July
Lobar pneumonia	9	15	9	6	13	6	5	3
Bronchopneumonia	4	10	16	8	2	2	2	–
	13	25	25	14	15	8	7	3

Infants. Forty-one infants had primary pneumonia. The clinical diagnosis and differentiation between lobar and bronchopneumonia were confirmed by X-ray examination in 35 cases. Twenty-three were male and 18 female. Lobar pneumonia was present in nine cases and bronchopneumonia in 32. The various types of pneumococci which were identified are shown in Table III.

TABLE III

Types of Pneumococci Isolated from 41 Infants with Primary Pneumonia

Pneumococcal types	I	II	III	IV	V	VI	IX	X	XII	XIV	XVIII	XIX	XXIII	XXV	None
Number of cases															
Lobar	2	1	–	1	1	1	–	–	–	–	–	1	–	–	2
Bronchial	3	1	5	–	–	1	1	1	3	2	2	–	1	1	11
Totals	5	2	5	1	1	2	1	1	3	2	2	1	1	1	13

Type XXII was associated with Type IV and Type XIX with Type V.

In all, 28 cases of pneumonia yielded pneumococci, β-haemolytic streptococci were found in association with the pneumococcus in one case, and found alone in another. No pathogen was recovered in 12 on first or repeated examination, but these cases are included amongst the primary pneumonias because they were essentially similar to the primary pneumococcal pneumonias in their clinical features. It will be noted that Types I, II, and III together were found in 12 of the 28 cases. This proportion is unusually high, and at variance with the general experience that the pneumococci mainly responsible for the pneumonias of infants belong to types other than I, II, and III. By contrast, Types XIV and VI, and perhaps XIX and XVIII, occur less frequently than one is led to expect from the results of other series.

The main clinical findings are given in Table IV, which shows that 17 of the infants were below one year and 24 were between one and two years of

TABLE IV

Classification, Age Distribution, Complications, and Fatality Rate of Primary Pneumonia in Infants

Classification	Number of cases	Age		Complications		Deaths	Case fatality rate %
		0 to 1 yr.	1 to 2 yr.	Otitis media	Empyema		
Lobar pneumonia	9	1	8	1	1	1	11
Bronchopneumonia	32	16	16	1	–	1	3
All pneumonias	41	17	24	2	1	2	5

age. All the infants under one year with one exception had bronchopneumonia, whereas one-third of the number over one year of age had the lobar form. The empyema occurred in an infant aged 21 months who did not respond to treatment with sulphapyridine, and died after rib resection. A Type I strain was isolated from the pleural pus. The numbers are so small that no conclusions may be drawn from them, but the low case fatality rate of 5 per cent. may reasonably be ascribed to the use of sulphapyridine. The age distribution of the two forms of pneumonia in infancy, and the importance of the pneumococcal type in relation to complications, will be discussed later.

Thirty-two cases, five lobar and 27 bronchopneumonia, were treated with sulphapyridine (see Table V). Twenty reacted to the drug within 48 hours, while eight treated on a comparable basis did not do so, but ran an extended

TABLE V

Response to Sulphapyridine

	Number of cases	Number treated	Responded within 48 hr.	Did* not respond	Results* not assessable	Sulphapyridine-treated case fatality rate %
Lobar pneumonia	9	5	4	1 (1)	—	20
Bronchopneumonia	32	27	16	7 (1)	4 (0)	4
Totals	41	32	20	8 (2)	4 (0)	6

* The figures in parentheses indicate the number of deaths.

course for a variable number of days, very similar to the nine cases which were given no specific treatment.

No comparison can be made between the effectiveness of the drug in the two forms of pneumonia. It is noteworthy that of the five pneumonias from which a Type I strain was isolated, four were included in the group which did not respond. Other pneumococcal strains found in this group were Type III in two cases and Types XII and XVIII in one each. By contrast, satisfactory responses were observed in three Type III pneumonias, two Type XII and one Type XVIII. It will be noted that the case fatality rate of 6 per cent. for the sulphapyridine-treated is higher than the rate of 5 per cent. for the treated and untreated taken together. The reason for this is that the untreated cases were milder, and all recovered, whereas the treated group included all the patients who were seriously ill. There was a recurrence of fever after the drug was stopped in two pneumococcal pneumonias (Type I and Type III). A toxic effect was noted in only one case, where a morbilliform rash appeared on the fifth day after the administration of 5·5 gm. of sulphapyridine.

Children. Twenty-five children between two and 12 years of age had pneumonia. The clinical diagnosis was confirmed by X-rays in 21. Thirteen were male and 12 female. Lobar pneumonia was present in 16 cases and bronchopneumonia in nine. The types of pneumococci found are shown in Table VI.

TABLE VI

Types of Pneumococci Isolated from 25 Children with Primary Pneumonia

Pneumococcal types	I	II	III	VI	VII	VIII	XIV	XVIII	XXIX	XXXII	None
Number of cases											
Lobar	1	1	1	2	1	1	1	1	1	1	5
Bronchial		2				1					6
Totals	1	3	1	2	1	2	1	1	1	1	11

Type VIII was associated with Type XIV and Type VI with Type I.

Pneumococci of various types were obtained from only 14 out of 25 cases of pneumonia in this group, while no pathogen was identified in the remaining 11 cases.

TABLE VII

Classification, Complications, and Fatality Rate of Primary Pneumonia in 25 Children

Classification	Number of cases	Complications		Deaths and fatality rate
		Otitis media	Empyema	
Lobar pneumonia	16	–	1	0
Bronchopneumonia	9	1	–	0
All pneumonias	25	1	1	0

The children with lobar pneumonia were distributed fairly evenly throughout the 2 to 12 year age period. Seven of those with bronchopneumonia were between two and three years old, one was three, and one was four years.

The empyema occurred in a girl of 4½ years with a Type III pneumonia which did not respond to sulphapyridine. No organism could be grown from the pleural pus.

Twenty cases, 13 lobar and seven bronchopneumonia, were treated with sulphapyridine. Fourteen reacted satisfactorily within 48 hours. Three did not do so, of which one was a lobar pneumonia from which a Type III strain was isolated, and two were bronchopneumonias which did not yield organisms of pathological significance. These three cases resembled in their clinical course the five cases not given sulphapyridine.

TABLE VIII

Response to Sulphapyridine

	Number of cases	Number treated	Responded within 48 hr.	Did not respond	Results not assessable	Sulphapyridine-treated case fatality rate %
Lobar pneumonia	16	13	9	1	3	0
Bronchopneumonia	9	7	5	2	–	0
Combined totals	25	20	14	3	3	0

There were no deaths. The mortality from pneumonia in childhood is naturally low, so that the favourable results cannot be attributed to sulphapyridine with the same confidence as in infancy, where the mortality was high before this form of treatment was used. No recurrence of fever was noted after the drug had been stopped; toxic effects consisted of a morbilliform rash on the 10th day of illness after 16 gm. of sulphapyridine in a patient who did not respond, and a morbilliform rash accompanied by severe haematuria on the fifth day after 12 gm. in a boy aged five years. The haematuria soon ceased when the drug was stopped and the fluid intake increased.

Discussion

Forty-one infants and 25 children had primary pneumonia. Twenty-five (38 per cent.) of the whole group of 66 cases were lobar, and 41 (62 per cent.) were bronchopneumonia. Sixteen children and nine infants made up the lobar group. Only one of the nine was below one year of age. Thirty-two of the 41 cases of bronchopneumonia were in infants as against nine in children. Sixteen of these infants were below one year, and all the children were below five years. In reviewing these figures it should be borne in mind that owing to air-raids there had been a mass migration of children, mainly over five years of age, from the area served by the hospital. The incidence of lobar pneumonia might otherwise have been considerably higher.

Clinical types of pneumonia. Bronchopneumonia is a disease of infancy. Over the age of three or four years it becomes uncommon and most primary pneumonias assume the lobar form, till old age is reached. McNeil's (1939) figures provide a good illustration. Reviewing 464 cases of primary pneumonia in childhood which occurred in Edinburgh between 1931 and 1938, he states

that 359 were lobar and 105 were bronchial in type. Ninety-five of the latter affected infants, so that there were only 10 cases of bronchopneumonia in children above two years of age, compared with 226 cases of the lobar variety. Some doubt still exists as to the relative frequency of the two forms in infancy, partly because of the difficulty of differential diagnosis, even with the help of X-rays, and partly because lobar pneumonia in an infant or young child may be comparatively benign, and so be mistaken for bronchitis and treated at home, while practically all cases of bronchopneumonia show more or less severe constitutional effects and are sent to hospital. Bronchopneumonia is more fatal to infants than lobar pneumonia, so autopsy statistics may give a misleading impression of the incidence of the two varieties of the disease. Blacklock and Guthrie (1933), indeed, reported only 12 definite cases of lobar pneumonia in 140 children, 112 of whom were under three years, but the reports of other authors do not show this marked preponderance of bronchopneumonia even for the first two years of life. Reimann (1938) cites 737 cases of primary pneumonia in patients under two years, and 60 per cent. were lobar. In McNeil's (1939) series 228 of 464 cases of pneumonia affected infants and 133 (58 per cent.) of these were lobar. Bronchopneumonia, however, was preponderant during the first year of life (neonatal period excluded) when there were 64 cases to 51 lobar, while lobar pneumonia became preponderant during the second year, and after that was greatly in excess, as has been already stated. Other series are in line with McNeil's and Reimann's findings.

Isolation of the pneumococcus. Pneumococci were isolated from 42 of the 66 cases of pneumonia by use of the laryngeal or deep throat swab. The proportion from which pneumococci were isolated was smaller than in many of the recorded series, where for example up to 80 per cent. (Lindberg, 1941), 78 per cent. (Butler, 1941), and 83 per cent. by suction from the nasopharynx (Auger, 1939) have been found.

That the pneumococci recovered by laryngeal swab in our 42 cases of pneumonia were the aetiological agents is an assumption that could be substantiated only if the identical organism in each case had been isolated from additional sources, such as lung, blood, or pleural fluid. On the other hand the pathogenicity of certain pneumococcal types, such as I, II, V, and VII, has been so adequately and frequently established in adults that their responsibility is usually presumed when they are found, while Types XIV and XXII can be regarded as belonging to this group in the lobar pneumonias of young children. Types I and II are rarely found in the throats of normal children or adults except in contacts or carriers. Type I is uncommon in the pneumonias of infants, but becomes frequent in those of older children. Type II is also uncommon in infancy, and the relatively high incidence of Types I and II in our series is somewhat surprising, but perhaps to be explained by the fact that most of the infants had spent night after night in air-raid shelters in close contact with adults. The pathogenic role or otherwise of the pneumococcal types, other than those specified, isolated

from the throats of young children with pneumonia is not easily assessed, as they may be found frequently in perfectly healthy subjects. According to Cruickshank (1939), Types IV, VI, XIX, and XXIII are probably the predominant saprophytic pneumococci which, under suitable conditions, are most likely to be responsible for bronchopneumonia during the first few years of life. Yang (1941) found that 38 of 40 children in a nursery were carriers of pneumococci for weeks or months. Pfeiffer's bacillus was next in order, associated frequently with pneumococci, while haemolytic streptococci were rarely carried. Type VI was the commonest, and then Types XIX, XXIII, XXII, and IV. Type II was never found, and Types I and III but seldom. There was only one case of pneumonia during the period of observation. Lindberg (1941) isolated pneumococci from 45 per cent. of a batch of normal children and infants, 14 of the 32 types being represented. Types XIX and VI were most frequent, then XIV, IX, VIII, and II. Finally, Nemir, Andrews, and Vinograd (1936), reviewing 1,033 cases of pneumonia in children aged two weeks to 13 years, as well as 425 with upper respiratory infection or bronchitis without pneumonia, found that Type XIX occurred with equal frequency in both of these categories, that Types VI and III occurred more than half as frequently in patients without as in those with pneumonia, and that Types VI, XIX, and III alone were present in one-third of the 425 patients who did not have pneumonia.

Relative incidence of infective types. Little typing of the pneumococcus found in the pneumonias of children has been done in this country, which is to be regretted, as findings abroad do not necessarily apply here. Detailed studies of the bacterial aetiology of pneumonias in childhood continue to be published in the United States of America and are now usually combined with reports on the results of chemotherapy. In infancy, Type XIV seems to be the most common, while over the age of two years Type I becomes more frequent and Type XIV diminishes. The order of frequency of the other types is not so well defined, but some stand out, notably VI, XIX, VIII, and XVIII. Nemir, Andrews, and Vinograd (1936) found that in their large series Types XIV, I, and VI caused 42 per cent. of all cases; XIV was the most common under two years, fairly common from two to five years, and less frequent over five years. Type I was common in older children, XIX was found almost exclusively in pneumonia affecting infants, especially under one year, and Type VI was scattered throughout the years of childhood and frequent in the earlier years. They also noted that there was a low incidence of Types I, XIV, VII, and V in bronchopneumonia (13 per cent.) as compared with lobar pneumonia (48 per cent.). Bullowa and Greenbaum's (1937) observations over a period of five years on 539 pneumococcal pneumonias in children are similar to those of Nemir, Andrews, and Vinograd. They state further that Types VIII and XVIII were observed chiefly below six years and Type V between two and six years. Types III, IV, and VII which were frequently isolated, were uniformly distributed in all age groups. From an analysis of extensive data collected in America and

abroad, Heffron (1939*a*) concludes that the following types, in order of frequency, are most commonly found in the lobar pneumonias of infants and children—XIV, I, VI, V, and VII. In bronchopneumonia the order is VI, XIX, and XVIII. He also points out that the frequency of the different types varies markedly with age, Type XIV preponderating under three years and VI and VII over that age. The higher incidence of 'Group IV' in the pneumonias of infants diminishes as childhood advances, and the proportion of the Types I, II, and III increases. The high incidence of these types in our series, in itself without general significance, tends to support Auger's (1941) contention that 'pneumonia in children due to Type I pneumococcus is a serious problem and deserves special attention'.

Association of pneumococcal types with complications. Purulent otitis media complicated three cases, but bacteriological examinations were not made. The types belonging to 'Group IV' are isolated as a rule from the pus, and correspond with those from the larynx. Blacklock and Guthrie (1933) found that Group IV strains were present in 31 out of 33 cases of otitis media which were due to the pneumococcus in infancy and childhood. Empyema developed in two (3 per cent.) of the 66 cases, one in a Type I lobar pneumonia and one in a Type III. The former was in an infant who died and the latter in a child of 4½ years who recovered. The frequency of empyema amongst children varies in different series, but in general it is between 7 and 10 per cent. It is commoner in lobar pneumonia than in bronchopneumonia, and in infants and younger children than in adults. In Bullowa's (1937) series 3·4 per cent. of 1,712 children with pneumonia developed empyema compared with 3·1 per cent. of 4,416 adults. In Nemir, Andrews, and Vinograd's (1936) series 10 per cent. of 1,033 children with pneumonia developed empyema. The majority of all empyemas in children are due to Type I, and the rest to Types V, XIV, and VII. Blacklock and Guthrie (1933) found that Type I was responsible for 46 per cent. of 66 empyemata; nearly all the rest were due to Group IV. In Bullowa's (1937) series already cited, the complication affected 13 per cent. of Type I pneumonias, 11 per cent. of Type V, and then most frequently Types XI and VII. Carey (1941) records 20 empyemas amongst 300 infants and 313 children. They were due to Type I in 12 instances, and Types III, V, and VI accounted for one each. Auger (1941) found a total of 66 empyemas (7 per cent.) in 900 pneumonias. Thirty-nine of them were pneumococcal and 82 per cent. of the 39 were of Type I. Twenty-nine cases (4 per cent.) resulted from 731 pneumonias in children over one year of age at the Cook County Hospital in Chicago, and 62 per cent. of the empyemas were Type I (Butler, 1941). Cruickshank (1933) has drawn attention to the greater invasiveness of Type I pneumococcus as compared with Types II and III. Treatment as a factor in the reduction of complications may be limited to an assessment of sulphapyridine, as serum has been less used in children. Nothing positive can be said at present, but a scrutiny of recent series gives the impression that the drug has some prophylactic value in reducing the complication rate.

Treatment and fatality rates. Sulphapyridine was omitted in 14 of our cases for no special reason except that the patients did not appear to be seriously ill. Two were afebrile and one was removed on the day after admission. The types found in seven of them were II (two patients), IV, V, VI, IX, and XXXII. An average of 4½ days elapsed between admission and final defervescence. The response to sulphapyridine was satisfactory in 34 cases. Types found included II, VI, and also I, III, VII, VIII, X, XII, XIV, XVIII, XIX, XXV, and XXIX. An average of 28 hours in these cases elapsed between admission (commencement of sulphapyridine treatment) and the fall of temperature. The 11 cases which did not respond satisfactorily to the drug included Types I (four patients), III (three patients), XII, and XVIII, and for these an average of between five and six days elapsed between the giving of sulphapyridine and the termination of the acute infection. To be at all adequate, a properly constituted control series must exclude variables, and show similarities as regards age, sex, pneumonic variety, and pneumococcal type, and no inferences may be drawn from the above except the impression that sulphapyridine hastened recovery. Many reports show that the drug shortens the course of the pneumonia, but its chief value is the saving of life. The fatality rate before the introduction of the drug was high during early childhood and especially in the first year. Table IX taken from McNeil's (1939) paper gives a good illustration of the position in this country before chemotherapy.

TABLE IX

Age Incidence and Death Rates in Pneumonia of all Types

Age period	1921 to 1928			1931 to 1938		
	Cases	Deaths	Death rate %	Cases	Deaths	Death rate %
1 month to 2 yr.	270	105	39	228	68	30
2 yr. to 5 yr.	164	12	8	123	7	6
5 yr. to 12 yr.	115	6	5	113	3	3
Totals	549	123	22	464	78	17

The mortality rates have been remarkably altered by sulphapyridine. Two of our sulphapyridine-treated primary pneumonia patients died, a case fatality rate of 4 per cent. Both were pneumococcal, one Type I in a lobar pneumonia affecting an infant of 21 months of age. Empyema developed in this case and death occurred 17 days after rib resection. The other was an infant of 14 days with bronchopneumonia from whom Type III was recovered. Forty-one of the total cases occurred in patients up to two years of age, so that the case fatality rate for this age group was only about 5 per cent. None of the children above two years died. A few reports of many from the United States of America may be cited. At the Cook County Hospital (Raycraft, Motel, and Greengard, 1941) the mortality rate prior to chemotherapy for infants under one year of age in 1937 and 1938 was 32 and 31 per cent. respectively. In 1940, 200 infants were treated with sulphapyridine and the rate fell to 10 per cent., or 8 per cent. when deaths within 24 hours

of admission are excluded. Wagoner and Hunting (1941) report one death (Type I infection) in a series of 109 infants and children with primary pneumonia treated with sulphapyridine and sulphathiazole. Carey (1941) found that the total fatality rate, excluding deaths occurring less than 24 hours after admission, in patients under two years was 2 per cent., and over two years was 0·5 per cent. Some of his patients received sulphathiazole and others antipneumococcal serum in addition to sulphapyridine or sulphathiazole. Bullowa and Greenbaum (1937) give detailed findings of the fatality rates in respect of the different types in 262 infants and 277 children before sulphapyridine came into use. These will provide a useful comparison when equivalent statistics with the drug become available.

Summary and Conclusions of Part I

1. This section deals with primary pneumonia affecting 41 infants and 25 children, 66 cases in all. An attempt was made to determine the causal organism in each case from one or more laryngeal swabs. Blood cultures were done in 25 cases, on the fourth day on the average, and before sulphapyridine was started, but all were sterile.

2. Particular attention was paid to the type of pneumococcus isolated, Cooper's 32 types being used. The relatively high proportion of 17 (41 per cent.) of the 42 types isolated belonged to Types I, II, or III, and the remainder to Types IV to XXXII. This somewhat unusual preponderance of Types I, II, and III in children is thought to be due to their having led a shelter existence during air-raids, in close contact with adults.

3. Fifty-two cases were treated with sulphapyridine in addition to the usual supportive measures. The response was satisfactory in 34 and unsatisfactory in 11 cases. Among the cases which responded, an average of 28 hours elapsed between the first dose of the drug and the permanent lowering of temperature. This contrasted with an average duration of 4½ days for those not treated, and 5½ days for those who did not respond well to the drug.

4. Complications were few, as were the toxic effects of sulphapyridine. The general case fatality rate was 3 per cent. The sulphapyridine-treated case fatality rate was 4 per cent.

5. The series presented is so small that the results of themselves admit of no conclusions so far as the pneumococcal aetiology is concerned. The beneficial effects of sulphapyridine are in keeping with numerous reports already published.

6. The British and American literature concerning pneumonia in infants and children is discussed, with particular reference to the significance of the different pneumococcal types in the pneumonias of childhood.

7. It is considered that the typing of pneumococci causing pneumonia in childhood in this country should be carried out on an extensive basis if the results of chemotherapy are to be intelligently assessed.

II. *Primary Pneumonia in Adults*

Forty-four adults had primary pneumonia. Bronchopneumonia was the clinical and radiological diagnosis in three patients, men aged 79, 52, and 42 years, from whose sputa β-haemolytic streptococci, H. influenzae, and pneumococcus Type XXIV were respectively isolated. All three were given sulphapyridine and all recovered, but how far this was due to the drug could not be determined, as the temperature was but slightly raised and the signs and symptoms were slow to disappear in each case. The patient with pneumococcal pneumonia had acute cardiac dilatation and failure. Pulmonary oedema persisted for some weeks and the interpretation of the clinical signs in the lungs was difficult.

Details in the following tables will be limited to the 41 cases of lobar pneumonia. X-ray photographs obtained in 24 instances confirmed the clinical diagnosis. In the remaining 17, the clinical manifestations were unequivocally those of the disease. Thirty-five patients were male and six female. Pneumococci were isolated in 33 cases. The age distribution, complications, and fatality rate are shown in Table XI. There were few complications, the only empyema occurring in a youth of 19 years. Pneumococcus

TABLE X

Types of Pneumococci Isolated from 33 Adults with Lobar Pneumonia

Pneumococcal types	I	II	III	IV	V	VI	VII	VIII	IX	XII	XX	XXIII	XXIX	Untypable
Number of cases	6	5	2	5	1	1	1	3	2	3	1	1	1	1

Type I was associated with Type VIII in one case, Type IV with Type I in another, and Type XI with Type XXIII.

Types I, II, and III comprised 41 per cent. and Types I to VIII 75 per cent. of those which could be identified. No recognizable pathogen was obtained from the eight cases which did not yield a pneumococcus.

TABLE XI

Age Distribution, Complications, and Fatality Rate in Lobar Pneumonia in Adults

Number of cases	Under 40 yr.	Over 40 yr.	Sterile pleural effusion	Empyema	Lung abscess	Abdominal abscess	Deaths	Case fatality rate %
41	18	23	2	1	1	1	3	7

Type VIII was found in his sputum and in the pleural pus, and was considered to be the causal strain, although Type I was associated with Type VIII in the sputum. The lung abscess appeared in a Type I pneumonia in a man aged 39 years. Pneumococcus Type XX was found on two occasions in the sputum of a man aged 68 years who developed an abdominal abscess. These cases will be referred to in more detail in the discussion.

The number of cases below the age of 40 years is contrasted with the number above 40, because the death rate above that age is invariably higher,

whatever the treatment. Two of the patients who died were over 40 years and neither had been given sulphapyridine. One was of a man of 69 years with a Type III pneumonia. Autopsy showed consolidation of the left lower lobe with bronchiectasis, and bronchiectasis in the right upper lobe, as a probable sequel to bronchopneumonia one year previously. There was an early adenocarcinoma of the pylorus. A culture from the left lower lobe gave a growth of H. influenzae and Streptococcus viridans, but no pneumococcus. The other patient, aged 50 years, was afebrile on admission, and died suddenly, 48 hours later. Apart from consolidation of the right lower lobe, nothing significant was found at autopsy, but the brain was not examined. No causal organism was isolated. The third patient who died was under 40 years; he was the youth mentioned above who developed empyema. He had been treated with large doses of sulphapyridine.

TABLE XII

Response to Sulphapyridine

Number of cases	Number treated	Responded within 48 hr.	Did not respond	Results not assessable	Deaths	Sulphapyridine-treated case fatality rate %
41	30	20	6	4	1	3

Eleven patients were not given sulphapyridine in hospital, and there were no deaths in this group. Four had been given the drug at home and were afebrile on admission. Five others, also afebrile when admitted, had not been given the drug at home. Two were febrile but obviously recovering. Twenty out of 30 patients given sulphapyridine in hospital responded to the drug within 48 hours. In four others it could not be decided whether recovery was associated with this treatment. In six cases the course of the disease was unaffected by sulphapyridine, and one, the patient with empyema, died. The pneumococcal types in this group were I (two cases), II, IV, VIII, and none. Strains of similar types were found in the group of cases which responded satisfactorily. The toxic effects noted were a rash in three cases, vomiting in one case, and marked depression in another. Two of the rashes were scarlatiniform, and they occurred on the 12th day of treatment after 39 and 59·5 gm. of sulphapyridine respectively. One rash was morbilliform and occurred on the seventh day after 39 gm.

Discussion

There were 44 cases of primary pneumonia in adults. Forty-one were lobar, and pneumococci were isolated in 33 of these. Types I, II, and III accounted for 13 of the 32 identifiable types. The number of pneumococcal pneumonias, incidence of individual types, and the mortality vary from year to year for a given community, but statistical studies show that there are broad characteristics and trends for different countries and geographical areas. Knowledge of the bacteriology of the pneumonias prevalent throughout Great Britain is far from complete. The systematic typing of pneumococci

has been undertaken in comparatively few centres, some of which are shown in Table XIII. Few studies of the incidence of the pneumococci apart from Types I, II, and III have been published in this country, and these have generally been referred to as belonging to Group IV.

TABLE XIII

Lobar Pneumonia in Adults: Number and Distribution of Cases by Type

Author	Year	Place	Number of cases	Frequency percentage			
				Type I	Type II	Type III	Group IV
Glynn and Digby (1923)	1919–21	Liverpool	96	45·8	22·9	2·1	29·2
Malloch (1922)	1920–21	London	67	35·8	14·9	3·0	46·3
Urquhart (1921)	1920–21	London	33	51·5	24·8	—	24·2
Grant (1922)	1922	Glasgow	38	31·6	60·5	5·3	2·6
Griffith (1928)	1920–27	London	278	34·2	24·1	5·4	36·3
Davidson (1925) and McLachlin (1925)	1924–25	Edinburgh	52	59·6	11·5	15·4	13·5
Ferguson and Lovell (1928)	1925–27	Manchester	116	43·1	4·3	—	52·6
Alston and Stewart (1930)	1929–30	Edinburgh	182	29·1	41·2	3·8	25·8
Pratt	1930	Glasgow	100	38·0	35·0	4·0	23·0
Smeall (1931)	1930–31	Edinburgh	60	20·0	58·0	—	22·0
Cowan, Harrington, Cruickshank, Cuthbertson, and Fleming (1932)	1930–32	Glasgow	737	37·6	34·6	4·2	23·6
Armstrong and Johnson (1932)	1931–32	London	160	33·7	30·0	1·9	34·4
Christie (1932)	1931–32	Glasgow	118	42·4	37·3	1·7	18·6
Christie (1933)	1932–33	Glasgow	60	23·3	53·3	11·7	11·7
Langley, Mckay, and Stent (1937)	1932–37	Salford	800	50·0	25·0	1·0	24·0
Davies, Hodgson, and Whitby (1935 *a*, *b*)	1932–33	London	137	40·1	9·5	14·6	35·8
Gaisford (1939)	1938–39	Birmingham	188	50·0	14·4	14·9	20·7
Don, Luxton, Donald, Ramsay, Macartney, Smith, and Adderley (1940)	1939–40	Manchester	200	43·0	20·0	13·5	23·5
		Total cases	3422				
		Weighted mean values		41·1	27·6	4·9	26·4

The table shows that Type I, with a percentage of 41·1 between the years 1919 and 1940, has been identified in the greatest number of lobar pneumonias at these centres as a whole, that those caused by Type III are few, while Type II and Group IV are about equal and intermediate in incidence. In Glasgow and Edinburgh Type II cases figure as prominently as Type I. An aggregate of cases from New York, Boston, Philadelphia and Baltimore, Chicago, and some of the eastern and southern States (Heffron, 1939 *b*) may be given for comparison. They are taken from series published during the past 20 to 30 years, and number 12,572 cases of lobar pneumonia, of which

31·2 per cent. were Type I, 17·8 per cent. Type II, 12·1 per cent. Type III, and 38·9 per cent. Group IV (weighted mean values). The distributions of the types in Great Britain and in the United States of America differ from one another to an extent which is not due to chance. The incidence of Types I and II is significantly greater in Great Britain than in the United States of America, but the reverse is true for Type III and Group IV.

The relationship of type prevalence and age is important. Together they constitute the most significant feature in the interpretation of mortality statistics. Type I, least common in infancy, increases during childhood, until it is present in the biggest proportion of cases of lobar pneumonia in earlier adult life (ages 20 to 40 years). Thereafter the number of cases due to this type declines steadily. Conversely, Type III, relatively infrequent before middle age, assumes an importance equal to that of Type I as the sixth decade is approached, and thereafter becomes increasingly preponderant. Our two adult patients with Type III were aged 57 and 69 years. Type II follows much the same frequency pattern as Type I. Group IV does not seem to have any characteristic variation from one age period to another.

Little is known about the incidence of Types IV to XXXII in this country. It is uncertain whether all of them can give rise to lobar pneumonia, but some are definitely implicated. According to Cruickshank (1939) Types V and VII are the 'epidemic types', and VIII, XIII, and XVIII the 'facultative pathogens' most likely to give rise to the disease, the latter types particularly in older and debilitated persons. Quite large series of pneumonia attributable to the types other than I, II, and III are available from America. Reporting 2,229 cases of lobar pneumonia in adults, Finland (1937) states that Types V, VIII, and VII account for 8·6, 7·2, and 5·7 per cent. respectively. Types I, II, and III together accounted for 57·5 per cent. His findings in 339 cases of lobar pneumonia at autopsy are similar, Types I, III, II, VI, VII, VIII, and IV in order of frequency, were found in 91 per cent. Heffron's (1939 *a*) conclusions from a summary of extensive data are in essential agreement.

The bacterial aetiology of bronchopneumonia in adults is less well known. References to it in the British literature are few. Viruses, and organisms such as the haemolytic streptococcus, staphylococcus, H. influenzae, and the bacillus of Friedländer may be the cause alone, or may be in association with, or may precede invasion by, the pneumococcus. Nevertheless, the pneumococcus is apparently the infecting organism in a high proportion of cases. More of the pneumococci isolated in the atypical than in the lobar pneumonias belong to the types other than I, II, and III, but there is an element of uncertainty from the fact that many of the types isolated are saprophytes in the throats of healthy people. In his autopsy series referred to, Finland states that the types isolated included III, VIII, V, I, X, VII, VI, XX, and XVIII, these nine types comprising 68 per cent. of the total. The same author isolated pneumococci belonging to Group IV to the extent of 77 per cent. in a clinical series of 619 cases. Types I and II together

accounted for only 7 per cent. and Type III for 16 per cent. Heffron (1939 *a*) concludes that in adult bronchopneumonias the pneumococcal types in order of frequency are III, VIII, X, XX, XVIII, and VII.

The commonest complications of lobar pneumonia in adults are pleurisy and empyema. Less common are lung abscess, pneumococcal meningitis, venous thrombosis, chronic pulmonary fibrosis, and corneal ulceration. Serous pleural effusion has been noted more frequently since the introduction of the sulphonamides. In our small series, there was one empyema, one lung abscess, and one abdominal abscess. The empyema complicated a pneumonia, in which Type I was associated with Type VIII occurring in a youth aged 19 years who was very toxic on admission and did not respond to intensive chemotherapy. A sudden increase in the amount of fluid in the left pleural cavity (synchronous with a scarlatiniform sulphapyridine rash) displaced the mediastimum and caused severe pain in the liver region. The aspiration of two pints of pus had to be carried out while a noisy air-raid was in progress, and the patient immediately developed acute dilatation of the stomach, from which he ultimately died.

Lung abscess has been described as occurring in lobar pneumonia, with gangrene or independently of it. The former, as Heffron (1939 *c*) states, is probably associated with the presence of an anaerobic group of organisms, while the latter can happen with the pneumococcus alone, perhaps resulting from tissue necrosis due to impairment of the local circulation, or else direct cellular injury due to the organisms present. Our patient was almost certainly in this category, as his sputum was scanty, and never foul or typically 'prune-juice' or chocolate coloured. The patient was a man of 39 years whose temperature subsided, but never finally settled, after large doses of sulphapyridine. When the drug was stopped, the temperature mounted again and continued to swing between 98° and 102° F. He complained of pain in the right renal angle, but the urine, repeatedly examined, showed no evidence of infection of the renal tract. The X-rays showed a vague opacity over the upper half of the right lung, but no suggestion of a fluid level. No pus could be aspirated, although attempts were made at different sites on two occasions. There was little cough and no clubbing of the fingers, but marked nocturnal sweating. At the end of the seventh week of illness, the patient had a severe fit of coughing and brought up about 1 oz. of thick yellow pus, which was unfortunately lost in transmission to the laboratory. A Type I pneumococcus had been isolated from the sputum twice. Complete recovery was rapid and uneventful. An abdominal abscess was diagnosed in a man aged 68 years from whose sputum Type XX was isolated. Expectant treatment resulted in recovery in about two months. Serous pleural effusion was noted in two patients.

The general incidence of empyema in lobar pneumonia in adults is between 3 and 4 per cent. Empyema occurs more frequently when the organism is the haemolytic streptococcus (Heffron, 1939 *d*) than when it is the pneumococcus, but the greatest number of empyemas are pneumococcal

because the majority of pneumonias are pneumococcal. Of a series of 5,393 cases of pneumococcal lobar pneumonia collected by Heffron (1939 *e*) 5·3 per cent. developed this complication. A limited number of types have been found mainly responsible, including I, III, V, II, and VIII, which caused 78·5 per cent. of 247 cases described by Finland (1937). Type I caused 93 of his cases, Type III 37, and Type V 31. Type I, in fact, is more prominently identified with empyema than any other. Reports by Smeall (1931), Gaisford (1939), and Cruickshank (1933) substantiate this. Anderson and Cairns (1940) found that 6 per cent. of 47 Type I pneumonias developed empyema, 4 per cent. of 112 Type II, and 13 per cent. of 38 Type III. Of 255 Type I pneumonias reported by Cruickshank (1933) 4 per cent. developed empyemas as did 1 per cent. of 253 Type II, and 1·5 per cent. of 192 Group IV cases. Cruickshank's series is included in the aggregate of 5,393 cases of lobar pneumonia (various authors 1926 to 1937) collected by Heffron (1939 *e*) which shows that 5·3 per cent. of them were complicated by empyema, comprising 6·4 per cent. of Type I pneumonias, 4 per cent. of those due to Type II, 4·4 per cent. of those due to Type III, and 5 per cent. of the pneumonias due to pneumococci belonging to Group IV. Types V and VIII are the members of Group IV most often implicated. In the one case in our series where empyema occurred, Type VIII was isolated from the pleural pus and the sputum, and Type I was associated with Type VIII in the sputum. Whether chemotherapy has favourably influenced the frequency of empyema and other complications is not yet clear. The beneficial influence of the early use of serum in this regard is well known, and it remains to be seen whether the use of sulphapyridine at an early stage is of more prophylactic value than later.

Many factors, together or singly, affect the prognosis in pneumonia. These include season, sex, personal habits, previous health, occupation, age, social status, constitution, humoral defence mechanisms, variety and virulence of the invading organisms, the presence or absence of bacteraemia, the kind of treatment, and the stage at which treatment is instituted. The mortality from pneumonia has been falling steadily during the past half-century, but even so, the disease was one of the principal causes of death before the introduction of serum and sulphapyridine. In this country the fatality rate for lobar pneumonia was about 20 per cent., which was considerably lower than the figure for the United States (30 to 32 per cent.).

Types I, II, and III are responsible for the great majority of deaths due to lobar pneumonia. In Great Britain the percentage of deaths caused by Types I and II used to be in the neighbourhood of 10 to 15, and 20 to 30 respectively. The percentage for Type III was 40 to 50, and for Group IV, 10 to 15 (Davies, Hodgson, and Whitby, 1935 *a*, *b*). Cruickshank (1933) has called attention to the fact that the progressive mortality in the first three types matches their production of soluble specific substance in that Type I produces the least amount of capsular polysaccharide, and Type III the most. In this connexion it may be significant that the antigenicity of Type I

is greater than that of Type II, which in turn is greater than that of Type III (Sehmidt, Hilles, Dettwiler, and Starks, 1940). In the United States of Ameriea the death-rates for all types are, or were, in exeess of those in this eountry. The mortality from the atypieal pneumonias is considerably higher than that caused by the lobar form.

There is, or has been, a remarkable relationship between age, type, and mortality. It has been observed that the fatality rate of primary pneumonia in the period of infaney is high. After the seeond or third year of life the rate falls to a low figure till adoleseence, when it begins to inerease, and beeomes higher with eaeh suceeeding decade. Types I and II aeeount for the majority of pneumonias in this eountry (50 to 75 per eent.), and as these types are predominant in the earlier half of life, they are responsible for the greatest number of deaths. Above the age of 40 years, the ease fatality rate for all types shows a steady inerease. The proportion of cases of pneumonia due to the dangerous Type III is eonsiderably less in this country than in the United States of Ameriea where deaths from this type begin to exeeed all others from the age of 45 or 50 years onwards.

Serum treatment has brought about a substantial reduetion in the mortality due to Type I, and to a lesser extent, to Type II, and also Types V, VII, and VIII. Where it was used, it redueed the deaths from lobar pneumonia Type I from approximately 10 to 15 down to 5 to 6 per cent., and those due to Type II from 30 to 20 or 25 per eent. (Great Britain). The results were much more favourable in those under 40 than over 40 (Medical Rescarch Counеil Rep., 1934). Type III pneumonias were little influeneed by serum.

Numerous reports bear witness to the remarkable power of sulphapyridinc in pneumonia. Evans and Gaisford (1938) in the first hundred cases treated had a fatality rate of 8 per eent. Later Gaisford (1939) eited 400 eases with a pereentage mortality of 6·5 per eent. The fatality rates in several eontrol series ranged around 22 per cent. The fatality rates for other treated serics in this eountry inelude Anderson and Cairns (1940) 7·6 per cent., Don, Luxton, Donald, Ramsay, Maeartney, Smith, and Addcrley (1940) 6·7 per cent., and in North Ameriea, Pepper, Flippin, Sehwartz, and Loekwood (1939) 7 per eent., Plummer and Ensworth (1939) 8·5 per eent., Finland, Spring, and Lowell (1940) 17·8 per eent., Dowling and Abernethy (1940) 11 per eent., and Winters, Rhoads, Fox, and Rosi (1941) 9 per ecnt. In most of these series, deaths within 24 hours of admission have been exeluded from the reckoning. The fatality rate for our series of 41 cases was 7 per eent. If sulphapyridine-treated eases only are considered, the fatality rate was 3 per cent. Sulphapyridine has reduced the mortality for Types I, II, V, VII, and VIII, to an even greater extent than serum (Dowling and Abernethy, 1940). The results with Type III are also better with the drug than with serum, although the rate is still high (Dowling, Abernethy, and Hartman, 1940; Finland, Spring, and Lowell, 1940).

Investigations are now being made to diseover whether, and in what eireumstances, the mortality due to all types, and especially Type III, can

be further reduced by a combination of both forms of treatment. Anderson and Cairns (1940) employed sulphapyridine and serum in a small number of Type II pneumonias and were impressed by the more rapid and natural clinical improvement as compared with the effect of the drug alone. Don, Luxton, Donald, Ramsay, Macartney, Smith, and Adderley (1940), on the other hand, did not find the combination of the drug with serum an advantage so far as could be judged from the limited number of Type I and II cases which they treated. It is satisfactory that the drug appears to bring about a substantial reduction of the mortality in the older age groups as well as the younger (Finland, Spring, and Lowell, 1940; Dowling and Abernethy, 1940). It was noted that 18 patients of our series given sulphapyridine before or after admission were under 40 years, and only one died. Eighteen were over 40 years, and none died. One below 40 years was untreated and survived, while four above 40 years were untreated and two died. Many authorities are not satisfied that the number of deaths amongst older patients has been reduced to the minimum possible with the use of sulphapyridine, and urge from their experience that a combination of sulphapyridine and serum is the more effective treatment above the age of 40 years (Winters, Rhoads, Fox, and Rosi, 1941; Dowling, Abernethy, and Hartman, 1940). Finally, certain investigators insist that the time factor—the institution of treatment at an early stage of the illness—is as important with sulphapyridine as with serum (Dowling and Abernethy, 1940; Winters, Rhoads, Fox, and Rosi, 1941).

Summary and Conclusions of Part II

1. Forty-four cases of primary pneumonia amongst adults were investigated. Forty-one of them were lobar and three atypical. Pneumococci were isolated from 34. Thirty-nine per cent. of the recognizable pneumococci isolated belonged to Types I, II, or III, and the remainder were distributed among the other types.

2. Thirty of the patients were given sulphapyridine. The response to sulphapyridine was satisfactory in 20, equivocal or not assessable in four, and unsatisfactory in six. The failure to respond was referable to strain as well as to type difference. There were few toxic effects.

3. Complications were few. The general case fatality rate was 8 per cent. Of the three patients who died, two did not receive sulphapyridine. The case fatality rate for the drug-treated cases was 3 per cent.

4. The relationship of pneumococcal type to the pneumonic infection, its complications, mortality, and treatment are discussed, with reference to the more recent British and American literature.

5. The general results of drug therapy are satisfactory, but further inquiry should be made into the response connected with individual types of pneumococcal pneumonia, so that in time chemotherapy may become still more effective and economical in use. Typing of pneumococci should be done to a greater extent than at present in this country.

III. *Pneumonia Secondary to Measles*

Twenty cases of pneumonia in infants and children accompanied or followed measles. Thirteen were in infants and seven in children. Three of the infants were under one year, and 10 were over one year of age. Five of the children were between two and three years of age, one was three years, and one five. Pneumococci were isolated from 13 cases; no organism of pathological significance was found in the remaining six. The types of pneumococci found are shown in Table XIV. The β-haemolytic streptococcus was isolated from two

TABLE XIV

Types of Pneumococci Isolated from 20 Infants and Children

Pneumococcal types	I	II	III	IV	VI	VII	VIII	IX	XXIV	None
Number of cases	1	1	1	3	2	1	1	2	1	7

cases only, one in association with pneumococcus Type III and one independently. Table XIV shows that more than 75 per cent. of the strains found belonged to the types other than I, II, and III.

The lobar form of pneumonia was present in four of the infants, according to clinical and radiological evidence. The bronchopneumonic form was present in the remaining infants and all the children. There were no complications such as otitis media or empyema, and no case was fatal.

TABLE XV

Measles Pneumonia in 20 Infants and Children

Response to Sulphapyridine

	Number of cases	Number treated	Response within 48 hr.	Did not respond	Results not assessable	Deaths
Lobar pneumonia	4	4	4	–	–	0
Bronchopneumonia	16	13	10	1	2	0

The case which did not respond to sulphapyridine was of bronchopneumonia in a child aged two years. The temperature remained elevated for the eight days during which the drug was given, and fell to normal on the 14th day of illness. Type VI pneumococcus was cultured from the laryngeal swab. The same type was found in a case not given the drug, where the temperature became normal on the seventh day of illness. In the two cases where the effects of sulphapyridine were not assessable, the fever due to the bronchopneumonia had apparently been reduced by the drug when the measles rash broke out. The temperature promptly rose with the appearance of the exanthem and the signs of pneumonia persisted for some days afterwards. No toxic effects due to the drug were observed, and all the patients recovered.

Discussion

It is generally accepted that measles is a virus disease and that complications are due to subsequent invasion by one of, or a mixture of, organisms such as streptococci, pneumococci, staphylococci, or H. influenzae. The haemolytic streptococcus has for long been considered the organism chiefly

responsible for pneumonia in measles. It was the pathogen most frequently isolated by MacCallum (1921) in a great epidemic of pneumonia after an outbreak of measles in army camps in 1917–18. Hodes, Stifler, Walker, McCarty, and Shirley (1939) cultured the haemolytic streptococcus in association with pneumococci from the nasopharynx in 18 out of 38 of their patients, and Ellison (1931) found it alone, or in association with Pfeiffer's bacillus or the pneumococcus, in a considerable proportion of 74 cases. H. influenzae, and not the streptococcus, appeared to be the cause of the larger number of Ellison's cases of pneumonia, as it was present to the extent of 46 per cent., and in pure culture in 31 per cent. The infection with this organism induced a heliotrope cyanosis similar to that of the influenza pandemic of 1918. Pneumococci were found in 28 per cent. of his cases, alone or in association with the organisms already mentioned. Ellison (1931) concluded that the most benign cases are those in which pneumococci alone are present and that the prognosis is far worse where haemolytic streptococci are present alone or in combination with Pfeiffer's bacillus.

In our 20 cases of measles pneumonia, the haemolytic streptococcus was inconspicuous, being found twice only. Pneumococci were isolated in 13 cases as detailed above. Hodes, Stifler, Walker, McCarty, and Shirley (1939) made a systematic study of the pneumococcal nasal flora in 38 infants and young children with measles pneumonia, and isolated the pneumococcus in every case. Type XIV was isolated 11 times. Other types were II, III, IV, VI, VIII, XI, XV, XVI, XVII, XVIII, XIX (six times), XXIII (three times), and XXIX. Type XIX was next in frequency to Type XIV. Purulent otitis media developed in only one patient after treatment was started, and none of the patients had empyema. This absence of complications is in keeping with our experience. Ellison (1931) drew attention to the small number of cases of empyema in measles pneumonia in children, contrasting the greater frequency of empyemas amongst children with primary pneumonia and amongst adults with measles pneumonia, and attributes this to the comparative rarity of pneumonia due to the streptococcus in young children. An infant aged five months under our care developed scarlet fever, followed by pneumonia and empyema. The haemolytic streptococcus was isolated from the throat and from the pus. The patient subsequently died.

Our experience may resemble that of Hodes, Stifler, Walker, McCarty, and Shirley (1939) in a further point of treatment. These authors found that their cases of measles pneumonia reacted more quickly to sulphapyridine than a group of primary pneumonias. The temperature reached normal 10 hours sooner than in their primary cases. The average time which elapsed between the giving of the first dose of sulphapyridine and the fall of temperature to normal in our 34 primary pneumonias which reacted satisfactorily was 28·2 hours, and the equivalent figure for 14 treated cases of measles pneumonia was 22·6 hours, but this difference of 5·6 hours, when tested for significance, was found to be no greater than that which could arise by chance. The cases which did particularly well were the four lobar

eases, as they reacted in 16 hours on the average. Hodes, Stifler, Walker, McCarty, and Shirley (1939) gave a larger initial dose to their measles pneumonias than to their primary eases. They had no deaths in their series. We gave the same dose in both forms, and none of our cases died. In view of the fact that the pneumonia of measles usually causes an illness lasting 10 to 14 days or longer, and that about 80 per cent.[2] of the deaths in measles are due to it, the results of sulphapyridine must be considered most gratifying. The role of the pneumococcus, the streptococcus, and other organisms in the complications of measles merits further study.

Summary and Conclusions of Part III

1. Twenty cases of pneumonia associated with measles are described, four in infants being of the lobar variety, and the remainder bronchopneumonia.

2. The haemolytic streptococcus, contrary to general experience, was found in only two of the cases, while pneumococci of various types were found in nine.

3. Sulphapyridine was given in 13 eases, the response being satisfactory in 10, equivocal in two, and unsatisfactory in one. The nature of the response could not be correlated with the identification of particular organisms, as those patients from whom no organism was isolated responded as well as those who yielded pneumococci or streptococci.

4. There were no complications, no toxic effects due to the drug, and no deaths.

5. References are made to the relevant literature dealing with the bacterial aetiology in pneumonia in measles, and to the results of similar treatment.

6. In view of the good results with sulphapyridine, it is concluded that the drug should invariably be administered in measles pneumonia.

7. Fuller inquiry is necessary into the pathogenic role of the various organisms, particularly the pneumococci, isolated from the cases.

IV. *Pneumonia Secondary to Pertussis*

There were nine cases of bronchopneumonia secondary to pertussis, three in infants and six in children. Six were male and three female. All the children were under five years.

Pneumococci were isolated from five cases. The types identified were IV in two cases, and VI, XII, and XVI in one each. Type XIX was associated with Type VI. The β-haemolytic streptococcus was not found.

The cases of pneumonia were uncomplicated by otitis media or empyema, but convulsions were terminal events in the two patients who died, one of whom had not been given sulphapyridine. This was a female infant of nine months in a state of emaciation after whooping for seven weeks, in whom pneumonia had been present for about three weeks. A Type IV pneumococcus was isolated from the laryngeal swab. Death occurred three days

[2] The mortality at ages 0 to 5 years from measles in London during 1934–7 was 129 per 100,000.

after admission, but no autopsy was obtained. The other fatal case had been given sulphapyridine and will be referred to below. The case fatality rate in this small series was 22 per cent.

Eight infants and children received sulphapyridine, and the results are shown in Table XVI.

TABLE XVI

Bronchopneumonia in Nine Infants and Children

Number of cases	Number treated	Response within 48 hours	Did not respond	Deaths	Sulphapyridine-treated case fatality rate %
9	8	5	3	1	13

Sulphapyridine was given to eight of the nine cases. Five of the patients reacted to the drug. Two were seriously ill with pneumonia, one was moderately ill, and two were mildly ill. Despite the fall in temperature the lung condition did not improve quickly in four of the cases, for the consolidation was slow to disappear, and rales and crepitations persisted for several weeks.

Three cases did not respond. Two of them recovered, a Type IV strain being isolated from one, and no pathogen from the other. The temperature remained elevated for 4½ and 5½ days respectively in spite of treatment with sulphapyridine. The pneumonia was extensive in both, and the pulmonary signs did not clear up till two weeks after admission in one and a month in the other. The third patient who did not respond to sulphapyridine died. He was a boy aged 4½ years who developed pneumonia while in the pertussis ward, and was late in coming under our care. He had been given sulphapyridine, but probably in insufficient doses, as the blood-level was only 1·6 mg. per 100 c.c. (free). He developed convulsions before death. No pneumococcus or other organism was found. An autopsy was refused.

No toxic effects due to the drug were observed.

Discussion

As in measles, the haemolytic streptococcus has been held responsible for the added pulmonary and other infections in whooping cough, but this organism was not obtained from any of our cases. We found pneumococci in five cases, all of them belonging to the types other than I, II, and III. What aetiological significance can be attached to them is problematical. Kohn, Rubin, and Hobart (1940) at the Willard Parker Hospital in a recent series of 33 pertussis pneumonia cases found the haemolytic streptococcus, staphyloccus aureus, and pneumococci to be the most frequent organisms obtainable from the throat and elsewhere. Blood cultures were positive in two, pneumococcus Type I in one case and the β-haemolytic streptococcus in the other. The pneumococcal types present were XIX, VI, I, VII, X, XI, XIII, XIV, XVIII, XX, and XXI. Kohn, Rubin, and Hobart (1940) state that three mild cases responded as did 11 of the 13 moderately ill, while only three of the 17 seriously ill reacted to sulphapyridine. Five of the

group died. The organisms isolated were pneumococci and staphylococci or streptococci, Pfeiffer's bacillus or H. pertussis. No relationship was obvious between the flora and the degree of response. Kohn, Rubin, and Hobart (1940) used much bigger initial doses of sulphapyridine than we did, as much as 2·0 gm. for infants weighing less than 11 kg., although their maintenance doses were constructed on the same basis of 0·2 gm. per kg. of body weight. They suggest that H. pertussis, the presumptive pathogen in pertussis, may account for the lack of response to the drug in some of the cases complicated by pneumonia.

Summary and Conclusions of Part IV

1. There were nine cases of pertussis pneumonia affecting infants and children, and pneumococci were isolated from five of them. The pneumococci belonged to the types other than I, II, and III, and their aetiological significance is doubtful. The haemolytic streptococcus was not identified in any case.

2. There were no complications, and no toxic effects attributable to sulphapyridine.

3. Sulphapyridine was given to eight cases. The response was not satisfactory in three cases, one of which died. One case not given the drug died. In most of the cases, whether the temperature response was satisfactory or not, the resolution of the lung condition was considerably delayed.

4. It is concluded that sulphapyridine does not act with the same efficiency in pertussis pneumonia as in pneumonia complicating measles or in primary pneumonia. The reasons for this are not clear and require further investigation.

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THE PATHOLOGICAL CHANGES IN THE BRAIN IN FATAL HYPOGLYCAEMIA [1]

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With Plates 11 to 13

Introduction

Hypoglycaemia arising in the course of insulin treatment for diabetes and schizophrenia has aroused considerable attention in recent years, and numerous publications have appeared on the clinical symptoms, the brain changes, and the mechanism of their production. Interesting problems arise regarding both the metabolism and pathology of the brain. As nervous symptoms predominate, most attention has been directed to the histological nerve changes in fatal cases, and animal experiments have also been carried out to elucidate their mechanism, but no unanimity has been reached either on the pathological lesions or their interpretation. We propose in this paper to describe our findings in six fatal cases and to use them as a basis for reviewing the whole subject. The literature is already too extensive to be treated in detail and will be grouped in relation to the theories advanced to explain the pathological changes.

Gross vascular lesions were the predominant brain changes described in the studies published by Ehrmann and Jakoby (1924, 1925), Schereschewsky, Mogilnitzky, and Gorgaewa (1929), Dünner, Ostertag, and Thannhauser (1933), Schleussing and Schumacher (1934), Baker and Lufkin (1937), Baker (1938), Kastein (1938), Doering (1938), Sahs and Alexander (1939), and Jansen and Waaler (1940, case 6). The above authors described large haemorrhages and softenings in the meninges and brain. In some instances widespread degenerative changes of the nerve-cells were also found which Baker and Lufkin (1937) discounted as post-mortem artefacts. In most cases with haemorrhage and softening, primary damage of the blood-vessels was absent, but Kastein (1938) found thrombosis of several venous sinuses and large arteries in his case. Jansen and Waaler (1940) suggested a possible thrombotic origin for the massive softenings and haemorrhages in their case, but found no direct evidence for this explanation. In experiments on dogs, Dünner, Ostertag, and Thannhauser (1933) produced widespread endothelial proliferation with and without ischaemic changes and haemorrhages. They compared this lesion with the vascular proliferation in the mamillary body characteristic of Wernicke's encephalopathy.

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In a very large group, including both human and experimental studies, gross vascular lesions were less conspicuous than widespread and often continuous necrosis of the cortex and other grey centres (Stief and Tokay, 1932*a*, 1935; Terplan, 1932; Bodechtel, 1933; Grayzel, 1934; de Morsier and Mozer, 1936; Leppien and Peters, 1937; Stief, 1937; Salm, 1937; Weil, Liebert, and Heilbrunn, 1938; Accornero, 1938; Cammermeyer, 1938; Tannenberg, 1939; Appel, Alpers, Hastings, and Hughes, 1939; Ferraro and Jervis, 1939; Winkelman and Moore, 1940). This necrosis was characterized by degeneration and destruction of the nerve-cells, by varying degrees of microglial, macroglial, and mesenchymal proliferation, and was often so widespread that Bodechtel (1933), Stief and Tokay (1932*a*, 1935), Weil, Liebert, and Heilbrunn (1938), and Winkelman and Moore (1940) could hardly find a normal nerve-cell in the central nervous system. This was particularly impressive in the carefully controlled experiments carried out by Winkelman and Moore (1940). On the other hand most of the authors pointed out that the areas of necrosis, though continuous in the cortex through one or more convolutions, ended more or less abruptly. Distinctly focal lesions identical in appearance with those occurring in vascular lesions were frequently described. Often the necrosis was situated around the bottom of a sulcus. The upper layers were usually more affected than the deeper layers, thus producing a pseudolaminar type of necrosis. The Sommer sector of Ammon's horn and the Purkinje cells of the cerebellum were often affected, the latter more seriously than any other area in some experiments on depancreatized dogs (Hédon, Loubatières, and Broussy, 1938). In some of the experimental animals of Stief and Tokay (1932*a*), however, the subiculum was more severely damaged than the Sommer sector. Bodechtel (1933), Stief and Tokay (1932*a*, 1935), and Cammermeyer (1938) report a distinct predilection for the small neurones in the putamen and caudate nucleus, while the large cells of these centres and the globus pallidus were less severely affected. In many papers insufficient detail and loose terminology make it difficult to assess the type of degeneration reported, but the principal changes described were Nissl's severe cell change, and homogenizing and ischaemic degeneration, while simple tigrolysis, Nissl's acute swelling, and nerve-cell selerosis were also mentioned. All the authors in this group refer to defective oxygenation of the brain tissue as the main cause of the necrosis. While the majority consider this to arise from vasomotor disturbances such as constriction or stasis, others have indicated intracellular anoxia as the cause of the necrosis (Meyer, 1938; MacKeith and Meyer, 1939; Weil, Liebert, and Heilbrunn, 1938; Ferraro and Jervis, 1939). Only the last-mentioned authors discuss the possibility that endothelial proliferation may also be instrumental in producing the ischaemic changes. A few workers, while recognizing the importance of vascular factors, postulate an additional direct toxic effect of insulin upon the neurones (Kastein, 1938; Leppien and Peters, 1937). Kastein (1938) speaks of a metabolic-toxic action and identifies this with the interference of the oxidative processes by insulin.

Other workers discount a vascular theory altogether and make other suggestions (Wohlwill, 1928; Terbrüggen, 1932; Nicolajev, 1937; Malamud and Grosh, 1938; Scheller and Stroebe, 1938; Kobler, 1938). Wohlwill (1928) regards alkalosis and possibly disturbances in water metabolism as the cause of the widespread severe nerve-cell change and amoeboid alteration of the glia which were found in his two cases. Malamud and Grosh (1938) described severe cell degeneration with increase of lipoid deposits in a diffuse distribution throughout the grey matter with a particular predilection for laminae 3 and 5 of the cerebral cortex, while in Ammon's horn the persistent part of the pyramidal layer was affected. Scheller and Stroebe (1938) reported fatty degeneration and microgliosis in the cerebral cortex, the caudate nucleus, and putamen. Kobler (1938) found varying types of cell degeneration throughout the cortex and other grey centres; within the cortex they were mainly in the third and fifth layers. They included Nissl's acute swelling and chronic change, hyperchromatosis of the nuclei with enlargement of the nucleolus, loss of staining affinity of the cytoplasm and, finally, a peculiar vacuolization of the nuclei. The last feature was particularly marked in the nerve-cells of the Sommer sector. In spite of the frequent occurrence of circumscribed empty spaces in the central, temporal, and calcarine regions, the author repudiated a vascular pathogenesis. Vascular changes such as are described by Stief and Tokay (1932*a*, 1935) occur, according to him, only after exceptionally high doses of insulin. He attaches great importance to the changes in the nucleus, in view of its high carbohydrate content. Nicolajev (1937) found, apart from proliferation, regressive changes of the glia which were more marked if the animal were killed after the onset of coma. He discussed the possibility that the changes in the glia may be secondary to the damage of the liver, in which he frequently found small foci of necrosis.

Terplan (1932), Bowen and Beck (1933), Moersch and Kernohan (1938), and Hassin (1939) emphasized the importance of oedema as the cause of widespread nerve-cell degeneration in hypoglycaemia. Hassin (1939) described liquefaction of the nerve-cells which was also found in patients dying from metrazol, barbiturate, phosphorus, arsenic, and strychnine poisoning. While he stressed the difficulty of the interpretation of histological changes, he thought that vascular changes or anoxemia were not likely to be of pathogenic importance. The cell change is not irreversible and may be combated by infusion of hypertonic solutions of dextrose or magnesium sulphate. The problem of the reversibility of brain changes has been the subject of experimental investigation by Schmid (1936). He produced coma, often with convulsions, in rabbits, restored the animals with glucose, and killed them after three weeks of this procedure, which is comparable with Sakel's treatment for schizophrenia. Apart from hyperaemia, only slight nerve-cell change of the type of Nissl's acute swelling and proliferation of the glia in the subpial layer and the brain stem were found. The Purkinje cells alone showed occasionally homogenization of the cytoplasm. The changes of the nerve-cells were regarded as reversible and as an

expression of the immediate effect of insulin in therapeutic dosage. All the changes were due, according to the author, to the excessive output of adrenalin in response to the injection of insulin.

There are reports of a widespread proliferation of the fibrous glia in the subpial layer, cerebral and cerebellar white matter, and the brain stem, with no spatial relationship to necrosis or cell degeneration (Schmid, 1936; Lemke, 1937; Baker, 1938, 1939 *a*; MacKeith and Meyer, 1939; Nicolajev, 1937). Schmid (1936) found it in animals treated with therapeutic doses of insulin. While some of the authors do not express any opinion on the nature of this gliosis, MacKeith and Meyer (1939) consider the possibility that it might be a primary reaction to defective oxygenation, comparable with the fibrosis of organs after mild stasis.

The important question has been raised whether the cerebral changes, particularly those of a vascular nature, are produced not by hypoglycaemia *per se*, but by the intermediary action of epileptic convulsions. Stief and Tokay (1932 *a*), Grayzel (1934), and Tani (1935) stated that unless convulsions occurred the animals showed no significant changes in the brain. Weil, Liebert, and Heilbrunn (1938) found no strict parallelism between the frequency of convulsions and the severity of the brain lesions, but they saw severe changes more often in the group of animals treated with high doses of insulin. In this latter group epileptic convulsions were more likely to occur.

Case Reports

Case 1. A woman, aged 30 years, was admitted on 13.8.39 to Guildford Hospital (Dr. Elmslie Campbell), transferred to King's College Hospital (Dr. Lawrence), and died on 31.8.39. She developed diabetes acutely at the age of 22 years. Insulin was always necessary and for some months before her death the dose was 16 units of zinc protamine insulin and 8 units of soluble insulin given together before breakfast. This enabled her to lead an energetic physical and mental life and she had no organic complications, but she was prone to occasional severe and unpredictable hypoglycaemic attacks, mostly at night. As she slept with her mother, the latter noticed these attacks early and cut them short by giving glucose.

In August 1939 she went on holiday to a country hotel and took her usual insulin, but much unusual exercise and unfortunately no extra carbohydrate. On 12 August she went to bed at midnight perfectly well, but could not be wakened at 9 a.m. by her friend. The latter, recognizing hypoglycaemia, but unable to give sugar through the clenched teeth, injected two doses of 0·5 c.c. of adrenalin, with slight improvement which enabled some honey to be given by mouth, but complete flaccid unconsciousness with snoring and groaning persisted. At noon 50 gm. of glucose were injected intravenously, but coma persisted although in another hour a catheter sample of urine showed a trace of sugar. Swallowing was by then possible, further sugar was given, and by the evening 5 per cent. of sugar in the urine and heavy ketosis had recurred, requiring more insulin and close supervision, for which the patient was admitted to Guildford Hospital. The maximal possible duration of the hypoglycaemia was 10 hours. The further management was difficult from the continued coma and the uncertainty of swallowing and absorbing

carbohydrate. Five units of insulin were given about every six hours with 20 to 30 gm. of glucose every three to four hours, and by this means moderate glycosuria and hyperglycaemia with minimal ketosis were maintained, although on one occasion further hypoglycaemia (blood-sugar 42 mg. per 100 c.c.) occurred for an hour. No fundamental change in consciousness occurred, but by the end of a week the temperature had risen to 101° to 102° F.; the pulse-rate was 78 to 104, and the respiration rate 16 to 24.

The patient was then transferred to King's College Hospital and fed by a nasal catheter through which glucose, milk, eggs, &c. were given. Six units of insulin were administered every six hours and by this means a blood-sugar of 200 to 400 mg. per 100 c.c. was maintained, with 2 to 4 per cent. of glycosuria, but no ketosis. A dose of 100 mg. of benzedrine was given with no effect. The general condition became progressively worse, but the heart action remained strong and her blood-pressure normal until death. Oral ulceration, cyanosis (relieved by oxygen), pulmonary congestion, and sloughing of the skin progressed day by day until she died on the 17th day of coma with a respiration rate of 40 and a temperature of 107·2° F.

The neurological abnormalities merit further description. In the first four days of coma the pupils were contracted and reacted slowly to light, and no ocular paralysis was noted. All tendon and skin reflexes were normal, including the plantar reflexes. Unconsciousness was complete, but the coma not profound and an occasional vague movement was made as if the patient resented examination. From the fourth to the eighth day the pupils became more dilated and reacted very sluggishly to light, but were never fixed. A doubtful extensor plantar response developed on the left side only (Dr. Elmslie Campbell). From the ninth to the 17th day complete incontinence, unconsciousness, and paralysis persisted, although on the ninth and 10th days she slightly resented attempts to open the mouth. The corneal reflex was active, the pupils equal, medium in size, and active to light. Sometimes the eyes were deviated to the right, sometimes to the left, and at one time one eye was deviated while the other remained central. The optic fundi remained normal. The abdominal reflexes were constantly absent, but the tendon reflexes varied. The right knee jerk was mostly present, the left more often absent, and at a time when both were absent the biceps reflexes were brisk. The plantar reflexes were usually extensor, sometimes indeterminate, but never flexor.

An autopsy was performed 24 hours after death. Macroscopically the brain showed considerable hyperaemia of the pia mater and intense congestion of the cortical veins. On section, no gross change could be seen except for widespread cavitation of the 'Swiss cheese' type within the white matter and basal ganglia. This was due to a profuse growth of the gas-forming *Cl. welchii* which was found inside the blood vessels and in the adjacent tissue. There was no inflammatory reaction to the bacillary invasion, so that it must have occurred immediately before or just after death. No cerebral arteriosclerosis was found, nor were there any large or small haemorrhages.

Microscopical examination of the brain. The outstanding pathological change was a widespread loss of nerve-cells in the cerebral hemispheres, with a corresponding microglial and neuroglial reaction. In the frontal cortex, where the degeneration was specially severe, wide areas were practically denuded of nerve-cells (Plate 11, Fig. 1). The transition between such areas and the less severely damaged cortex was quite sharp. In the latter the second and third layers were often most affected and the disappearance of these layers was especially frequent in the grey matter at the bottom of a sulcus. Even

in the best preserved areas there was a general thinning of all the cortical layers with considerable loss of the smaller nerve-cells (Plate 11, Fig. 2). In the parietal and temporal lobes the pathological change was less intense except in the Island of Reil and the Sommer sector of Ammon's horn, where the degeneration was complete. In the occipital cortex, on the other hand, the changes were on the whole slight, the cortical layers were much better preserved, and slight degeneration of the external layers was found only in the grey matter at the bottom of the sulci. Although the loss of the nerve-cells was the predominant feature in the severe lesions of the cortex, there were some grossly degenerated cells scattered throughout the neuroglial and microglial proliferation, which were most readily recognized in haematoxylin and eosin preparations and possessed distinctive features. The cell body, invisible in Nissl preparations, was shrunken and triangular, had a homogeneous or somewhat foam-like appearance, and took up the eosin stain in varying degree. The nucleus was also sharply triangular and darkly granular, while the nucleolus, surrounded by a ring of darkly staining granules, was swollen and displaced to the base of the nucleus. It stained faintly pink with eosin, but was unstained by the Nissl method. In a few of these cells the nucleus was elongated or irregular in shape, while in the smaller cells the granular formation was very dense and no nucleolus could be recognized. Small accumulations of darkly staining granules irregular in shape and with fragments of attached protoplasm were regarded as extreme forms of this cellular lesion which has been referred to in the literature as homogenizing cell change (Plate 11, Fig. 3, and Plate 12, Fig. 8). No other types of nerve-cell damage were found in the cortical lesions, and examples of the homogenizing change were infrequent except in the Island of Reil. In the more or less intact cortical regions the majority of the cells were normal in shape and form, but their protoplasm contained no Nissl granules, while the nucleus was darker than normal and slightly swollen; also Bielschowsky preparations revealed no distinct neurofibrillar network. It is possible that these changes indicated some cell damage, but their significance is difficult to assess in view of the clinical condition of the patient prior to death.

The macroglial proliferation in the affected regions of the cortex was considerable, but fibre production was entirely confined to the subpial layers. The cells, which varied greatly in size and showed no regressive changes, were frequently found in small clumps presumably at the points of disappearance of nerve-cells. The microglial reaction was also evenly spread throughout the affected cortex (Plate 11, Fig. 4). Elongated rod-shaped forms were most numerous, but there were all transitions in size and shape between these cells and some irregular asteroid forms. There were no compound granular cells. Some endothelial proliferation was occasionally observed in the walls of the small vessels, but otherwise there was no mesodermal reaction. In the caudate nucleus and putamen the majority of the small nerve-cells had disappeared, while those remaining showed homogenizing change. The macroglial and microglial reaction was considerable and there was also much endothelial and capillary proliferation. In the thalamus, brain stem, and cerebellum no definite pathological changes were observed. In the cerebral cortex there were also changes in the nerve fibres, and myelin preparations showed partial degeneration of the radial and tangential fibres, which corresponded roughly in intensity to the degree of nerve-cell damage. In the white matter, although the myelin stained darkly and normally, there was a widespread fibrous gliosis of greatest intensity in the deep parts and around the blood-vessels. This gliosis was present in all

parts of the cerebrum and cerebellum and also extended into the pons and medulla.

Summary of Case 1. The patient was a woman, aged 30 years, suffering from diabetes. She died after being unconscious for 17 days after an attack of hypoglycaemia of uncertain duration, but of less than 10 hours. Microscopical examination showed a diffuse and widespread disappearance of nerve-cells in the cerebral cortex, especially the frontal, central, and temporal regions, with a secondary macroglial and microglial proliferation. Similar changes were found in the caudate nucleus and putamen. Many residual cells in the affected areas showed homogenizing cell change. There was also a diffuse gliosis of the white matter. No gross vascular lesions or haemorrhages were present.

Case 2. A man, aged 47 years, was admitted to King's College Hospital on 3.1.40 (Dr. Lawrence), and died on 9.1.40. He had developed diabetes in 1937. With insulin, 50 to 60 units a day, he maintained full working efficiency as a railwayman, but suffered intermittently from flatulent dyspepsia. In November 1939 he developed jaundice and as this did not clear up in a few weeks he was admitted to King's College Hospital for investigation in January, 1940. On admission his urine contained bile pigments, 4 per cent. of sugar, but no ketone bodies, and his blood-sugar was 235 mg. per 100 c.c. at noon, on a morning dose of 36 units of zinc protamine insulin and 24 units of soluble insulin. His diet was regularized at 200 gm. of carbohydrate, 60 gm. of protein, and a minimum of fat. Twelve units of soluble insulin were added in the evening and 40 units of zinc protamine insulin and 32 units of soluble insulin given in the morning (84 units a day). On this treatment his urine cleared rapidly and he had a mild hypoglycaemic attack two nights later. The insulin was reduced to 64 units, but hypoglycaemia recurred in the night and morning with blood-sugar levels of 48 and 56 mg. per 100 c.c. An extra 40 gm. of glucose produced recovery, but a relapse took place next night when the blood-sugar, in spite of glucose and adrenaline, was 41 mg. per 100 c.c. Partial recovery followed, and a reduced dose of insulin, 48 units in all, was given, but two hours later unconsciousness recurred with heavy stertorous breathing. In spite of 100 gm. of glucose by mouth, coma persisted, but the general condition and pulse remained strong. He died suddenly as venepuncture was being made for the injection of more glucose. Complete coma had been present for 12 hours before death and had been preceded by relapsing hypoglycaemia with lucid intervals for 36 hours, but no convulsions occurred.

At autopsy, the pancreas was found to contain numerous stones and to be largely destroyed. The liver was slightly enlarged, but otherwise normal, as were the other internal organs. There was no noticeable arteriosclerosis. The brain examined after fixation showed no macroscopic abnormality.

Microscopical examination of the brain. This revealed widespread changes affecting principally the nerve-cells in the cerebral cortex and basal ganglia. In the former the cortical layers were intact, as only a small number of nerve-cells had completely degenerated and disappeared (Plate 12, Fig. 5), but few nerve-cells presented a normal appearance and in the second and third layers the majority showed the following changes. The cell body was pale, swollen, or vacuolated, but sometimes it was recognizable with Nissl staining only as a faint shadow. The nucleus was mostly pyriform or elongated, and had a coarse granular and dark appearance, while the nucleolus was rarely seen. Where the nucleolus could be detected it had

an indefinite outline and appeared to be disintegrating. Although an enlarged pale nucleolus was not present in these cells, we have regarded them as examples of early homogenizing change. In the deeper layers many smaller cells were similarly damaged, but the majority showed Nissl's severe cell change. They were round, swollen, and pale with a foam-like or vacuolated protoplasm and a dark or somewhat pyknotic nucleus. In some the nucleus had disappeared leaving a cell shadow, while in others the cell body was breaking down. Some of the larger cells showed early ischaemic change, but only a few typical examples of this lesion had occurred. Even in the best preserved cells in the cortex the Nissl granules were indistinct and Bielschowsky preparations showed degeneration of the intracellular neurofibrils. These severe pathological changes in the cortex were widespread throughout the frontal, central, and temporal areas, and in Ammon's horn they were not confined to the Sommer sector. In the occipital regions of the hemisphere the cells as a whole were much less severely damaged. There was no microglial and very little macroglial proliferation in the cerebral cortex. Both the macroglial and the oligodendroglial nuclei stained more darkly than normal, but otherwise showed no regressive changes.

In the basal ganglia the small cells of the caudate nucleus and putamen showed uniform homogenizing cell change and the larger cells Nissl's severe change. In the globus pallidus the cells on the whole were much better preserved, but in the thalamus cell damage of varying severity was widespread. The basket cells of the cerebellum all showed homogenizing changes similar to those already described in this case, while in the Purkinje cells the nucleus was darker than normal and the cell body swollen. In the brainstem the nerve-cells were better preserved than in any other region of the brain. No evidence of myelin degeneration was found throughout the brain, and no definite increase of neuroglia in the white matter, but the neuroglial nuclei everywhere stained more darkly than normal. Some degree of endothelial proliferation was occasionally observed in the smaller vessels, but petechial haemorrhages and focal softenings of the cerebral tissue did not occur.

Summary of Case 2. The patient was a diabetic aged 47 years. He died after 12 hours' coma which was preceded by relapsing hypoglycaemia with lucid intervals for 36 hours. Microscopical examination showed a diffuse and widespread degeneration of nerve-cells in the cerebral cortex, basal ganglia, and cerebellum. Homogenizing cell change and Nissl's severe cell change were the predominant types of lesion. There was no microglial and little macroglial proliferation, and no gross vascular lesions or haemorrhages.

Case 3. A man, aged 59 years, was admitted to the Cane Hill Hospital for Nervous and Mental Disorders on 11.4.38, and died on 21.5.38. Apart from a head injury at the age of 30 years which caused unconsciousness for two to three days, this patient had been quite well up to three years before admission, when he began to complain of attacks which varied considerably in frequency, character, and duration. In general the main features were as follows. He first experienced a pricking sensation in the legs, quickly followed by stiffness and loss of control, so that he staggered about or fell down. In some attacks kicking his legs about seemed to restore their function, but in others he collapsed, had clonic convulsions of the arms and legs for five minutes or so, became quite unresponsive, and was confused for a few minutes after recovery. In other attacks there were violent movements of the body and limbs, but he did not completely lose consciousness, although he was considerably confused. At times the patient experienced a queer feeling

which he could not describe and which caused him to run home or up and down stairs without more serious symptoms developing. At other times loss of consciousness was prolonged for several hours, although it is not clear whether this was always preceded by convulsive movements of the limbs. Details are also lacking as to the frequency of the earlier attacks, but he was able to continue his work up to one year before admission to hospital. In the previous few months attacks occurred daily, and he had become moody and depressed. In hospital the attacks seldom produced unconsciousness, but he was much confused, and seemed unaware of his limb movements. Sometimes he seemed to try to control the movements, and at other times remarked that he was going 'crackers'. No physical abnormalities were discovered, apart from some general arteriosclerosis and a blood-pressure of 150/100. The true nature of the attacks was not recognized. They became more frequent and severe, and on 17.5.38 after an attack for which Somnifaine was given he became semicomatose. The stupor continued throughout the next two days with varying intensity, and on 20.5.38 he became deeply comatose and remained so till his death on 21.5.38, four days after the first onset of this last attack.

An autopsy was performed 36 hours after death. A small well-encapsulated tumour was found attached to the lower border of the pancreas, and on microscopy was found to be an adenoma of islet tissue. The brain which was congested and hyperaemic showed on section a few small haemorrhages in the pons and also some pallor of the caudate nucleus and putamen.

Microscopical examination of the brain. In Nissl preparations examined with the low power pallor of the second and third layers was observed over wide areas of the cerebral cortex. This pallor was interrupted in some places by small bridges of more normal staining giving a garland-like appearance to the lesion. It seemed to be more pronounced in the grey matter at the bottom of the sulci (Plate 12, Fig. 7). In the parastriatal region the pallor extended into the deeper layers and contrasted strongly with the normally stained calcarine region. With higher magnification a diffuse loss of nerve-cells was noted in the pale areas of the cortex, but many degenerated cells, which for the most part showed typical homogenizing changes, were still recognizable (Plate 12, Fig. 8). In a few of these cells, however, the eosinophilic phase of the degeneration had already passed and only the granular debris of the nuclei remained visible. Besides the homogenizing type degeneration, a few examples of Spielmeyer's ischaemic cell change (Plate 13, Fig. 9) and also Nissl's severe cell change were occasionally encountered. In the deeper cortical layers all these types of degeneration were present, although here there was no definite loss of nerve-cells and many presented a normal appearance. In the Sommer sector and end folium of Ammon's horn the damage to the nerve-cells was particularly severe, contrasting strongly with the more or less intact resistant part of the pyramidal layer (Plate 13, Fig. 10).

Microglial and neuroglial proliferation, varying in intensity with the severity of the nerve-cell degeneration, was present in the affected cortical areas. Apart from a subpial gliosis there was little fibre formation. Some of the neuroglial cells had undergone amoeboid changes. The myelin throughout the brain was slightly rarefied, but no gross demyelination was seen. Artefacts, including Buscaino's grape-like structures, were a notable feature. The caudate nucleus and putamen were abnormally pale in Nissl preparations (Plate 13, Fig. 11) and showed intense degeneration, especially of the small neurons, many of which had disappeared, while those remaining showed

advanced homogenizing change. There was also satellitosis of the proliferated oligodendroglia in relation to the degenerating nerve-cells and some macroglial and microglial proliferation. The large cells of the caudate nucleus and putamen were often swollen, like those of the globus pallidus. The thalamus and the remaining centres of the basal ganglia and brain-stem showed no pathological change apart from some increase of lipofuscin. In the cerebellum most of the Purkinje cells had an indistinct nuclear structure and the cytoplasm stained only faintly in Nissl preparations. The small nerve-cells of the molecular layer showed typical homogenizing change. There were also some regressive changes in the macroglia. Proliferative phenomena of the macroglia and microglia were absent. The endothelial and adventitial elements of the blood-vessels had undergone some proliferation in the cerebral cortex. In the pons several small diapedetic haemorrhages of very recent appearance were present and also some hemosiderin pigment in the adventitial cells, apparently indicating older haemorrhages. There was also much formalin pigment in neighbouring nerve-cells.

Summary of Case 3. The patient was a man of 59 years who had suffered for three years from hypoglycaemic symptoms of increasing severity caused by an islet adenoma of the pancreas. He died after four days of relapsing and gradually deepening coma. Microscopical examination revealed diffuse and widespread degeneration of the nerve-cells in the brain. Many had completely disappeared and those remaining showed various stages of homogenizing, ischaemic, and Nissl's severe cell change. The Sommer sector, the parastriatal region of the occipital cortex, the caudate nucleus and putamen, and the molecular layer of the cerebellar cortex were particularly affected. A varying degree of macroglial and microglial proliferation was present. A few small and recent haemorrhages were found in the pons, but otherwise there were no gross vascular lesions.

Case 4. A man, aged 23 years, was admitted to the Warwickshire Mental Hospital on 20.4.38, and died on 21.11.38. There was nothing of note in his family or personal history. He developed mental symptoms in May 1937 which gradually progressed and led to his admission to hospital with the diagnosis of schizophrenia. Insulin treatment was begun soon after admission. Hypoglycaemic coma was produced on 22 occasions with a dose of insulin of approximately 300 units, and he had six convulsions during the treatment. On the day of his death he was given 338 units of insulin at 7 a.m. He appeared to react in the usual way and at 10.50 a.m. was considered to be in full hypoglycaemic coma. At 11.15 a.m. he was observed to be in a collapsed condition, his lips, ears, and extremities were cold and blue, the pulse hardly detectable, the respiration slow and feeble, and the pupils widely dilated. Death occurred at once despite energetic treatment, which included intracardiac injections of glucose, coramine, and adrenalin. The blood-sugar was not examined during the coma or at the time of the collapse.

At the post-mortem examination no abnormality was found in the internal organs on naked-eye examination, apart from some atheroma of the first part of the aorta and some congestion of the liver, spleen, and kidneys. Histological examination of the myocardium showed considerable fragmentation and segmentation, and also some hyaline degeneration of the muscle fibres. The brain showed a moderate degree of congestion and some flattening of the cerebral convolutions, but on section no macroscopic lesions were seen. The blood-vessels were normal.

Microscopical examination of the brain. Under low magnification the Nissl preparations of the cerebral cortex appeared normal except for a small area in the grey matter at the bottom of a sulcus in the parastriatal region, where the outer layers were paler than normal. Under high magnification, however, the nerve-cells in all regions of the cortex showed a great variety of pathological changes. Some resembled Nissl's acute swelling in that the tigroid bodies had disappeared and the enlarged swollen processes of the cell body were visible over long distances; others showed Nissl's severe type of cell degeneration with a swollen cell body and a granular nucleus completely surrounded by a clear vacuolated area. The residual protoplasm at the cell margin was not darkly stained, thus differing from the so-called 'water' change (Plate 13, Fig. 12). Typical specimens of homogenizing or ischaemic change were not seen, even in the area of pallor in the parastriatal region. Here the cells for the most part were very indistinct, but the nucleus was more readily recognizable, was granular, and often stained a diffuse greenish-blue with Nissl's stain. In the caudate nucleus and putamen the cytoplasm of the small cells was homogeneous and pale in Nissl preparations and stained better with eosin. The nucleus was round and contained many deeply stained granules which were sometimes arranged around a pale nucleolus, although in most cells the latter was not clearly recognizable. More advanced stages of homogenizing change were not seen.

In the large cells of the striate body and globus pallidus the cytoplasm was better stained, but the Nissl bodies were absent, while the nucleus, although of normal shape, was pale and somewhat opaque and had a rather enlarged nucleolus. The nerve-cells in the various nuclei of the thalamus showed changes similar to the large cells of the basal ganglia. There was only slight cell change in the grey centres of the brain-stem. The cells in the inferior olive and dentate nucleus had increased lipofuscin. The Purkinje cells of the cerebellum were pale, showed tigrolysis and indistinctness of the nuclear structure, and on the whole stained better with haematoxylin and eosin than by the Nissl method. Many of the smaller nerve-cells of the molecular zone showed homogenization of the cytoplasm and granularity of the rounded nucleus, most probably an early stage of homogenizing degeneration. In Ammon's horn circumscribed lesions confined to the Sommer sector were not present. No considerable proliferation of the neuroglia or microglia was seen, although many of the macroglial cells showed regressive changes of an amoeboid nature. Some swelling of the oligodendroglia had taken place. The walls of the cerebral blood-vessels were normal, but the capillaries and venules were often distended with red and white blood corpuscles. There were no diapedetic haemorrhages.

Summary of Case 4. The patient was a young man of 23 years suffering from schizophrenia. He died suddenly during the course of therapeutically induced insulin hypoglycaemia. Six major convulsions had occurred during the previous insulin comas. Microscopically the brain showed widespread changes in the nerve-cells corresponding to Nissl's acute and severe type of degeneration. Typical homogenizing cell change was not seen, although some alterations could be interpreted as an early stage of this process. Only one area of focal necrosis of the outer cortical layers was observed in the parastriatal area of the occipital lobe.

Case 5. A man, aged 20 years, was admitted to St. Bernard's Hospital for Nervous and Mental Disorders on 18.7.39, and died on 3.4.40. There was nothing of note in his family or personal history. He was quite well until

January 1939 when, after a severe attack of influenza, he developed mental symptoms. These progressed over the next few months and he was eventually admitted to hospital, with the diagnosis of schizophrenia with katatonic excitement. Insulin treatment was administered from the 1.8.39 for a period of three weeks, resulting in a fair remission of symptoms, followed by a relapse. A second course of insulin treatment was commenced on the 27.2.40. On the 7 March prolonged coma occurred in which complete recovery was delayed for several hours and was followed by the patient's having some difficulty in speaking for a few days. Treatment was continued and on the 30 March he was having 2¼-hour periods of coma without untoward effects. On the 2 April 110 units of insulin were given at 7.24 a.m. and light coma ensued at 9.30 a.m. This was allowed to continue until 11.45 a.m. and sugar was then given as usual. Recovery was delayed, and 200 c.c. of 33 per cent. glucose in saline with 3 c.c. of Betaxin were given intravenously at 12.20 p.m. The reflexes became normal, but he did not recover consciousness. At 3.30 p.m. a further 200 c.c. of glucose solution containing Betaxin were given, resulting in some recovery so that the patient talked at 5.30 p.m., but he was again unconscious at 7.0 p.m., and his pulse was 150. Lumbar puncture was performed, but no cerebrospinal fluid was obtained. Sugar was given by stomach tube regularly and he was again conscious at 10.20 p.m. The pulse-rate was then 120 and the temperature slightly raised. At 8 a.m. on the 3 April he was very drowsy with a pulse-rate of 120, and rapid respirations. Sugar was still being given at regular intervals. At 10.30 a.m. the pulse-rate was 140 and as there was evident dehydration, subcutaneous saline was commenced and he became more alert. The temperature was then 104° F. Cardiac failure became increasingly evident and by 3 p.m. oedema of the lungs had set in. A blood-transfusion was attempted, 250 c.c. of blood being given with little effect. He became unconscious again about noon, and death occurred at 8.30 p.m. 37 hours after the original injection. No epileptic convulsions occurred during the whole period of treatment.

An autopsy was performed 27 hours after death. There was considerable congestion in all organs, but the heart muscle was pale. Heart failure cells were found in the lung. The brain was very congested and on section after hardening numerous cysts of the 'Swiss cheese' type caused by post-mortem invasion by *Cl. welchii* were found in the cerebral and cerebellar white matter and also the basal ganglia. The spinal cord did not show macroscopic changes.

Microscopical examination of the brain. No gross changes were seen in Nissl preparations of the cerebral cortex under low magnification, except that in the frontal and temporal regions the third layer appeared somewhat empty of nerve-cells, as also did the end folium of Ammon's horn, although the Sommer sector was unaffected. The high power showed only slight changes in the nerve-cells. In the slightly pale areas examples of Nissl's severe change were numerous; a few of these cells had marked granularity of the nucleus, but fully-developed homogenizing or ischaemic lesions were nowhere present. Throughout the cortex many cells showed alterations closely resembling Nissl's acute degeneration in that the cell body was swollen and pale with its process visible over long distances, while the nucleus was also swollen and had a well defined nucleolus. In the cerebral cortex there was some general microglial and macroglial proliferation which varied greatly in intensity and was occasionally focally accentuated in some parts of the molecular layer. In the caudate nucleus and putamen the pathological changes were slight and similar to those seen in the cerebral

cortex. No significant changes apart from a varying degree of tigrolysis were observed in the globus pallidus, thalamus, brain-stem, spinal cord, or cerebellum.

A striking feature of this case was the considerable proliferation which had developed in almost all parts of the cerebral and cerebellar white matter. In Holzer preparations the gliosis was even visible to the naked eye (Plate 13, Fig. 13). It was composed of a loose network of delicate fibres for the most part independent of the macroglial cells, although many fibres were still in connexion with the astrocytes. This proliferation of the glia, which was often accentuated round the blood-vessels and in the neighbourhood of the ventricles, was not associated with any degeneration of the myelin or axis cylinders. In the brain-stem there was also a diffuse gliosis without loss of myelin.

Summary of Case 5. A young man of 20 years suffering from schizophrenia died during the course of insulin treatment after coma lasting 37 hours. Microscopically the brain showed widespread acute swelling of the nerve-cells, and in a few areas in the frontal and temporal regions Nissl's severe cell change. There was also some loss of nerve-cells, with microglial and macroglial proliferation in these areas. A diffuse widespread gliosis in the cerebral and cerebellar white matter and in the brain-stem was also found.

Case 6. A diabetic patient of 49 years died after being in hypoglycaemic coma for at least 36 hours. The full clinical and autopsy details are lacking, but some Nissl preparations from the cerebral cortex were available for study. These showed characteristic and widespread pathological changes. Under low magnification there was pallor of all the cortical areas, in some places extending throughout the entire depth of the cortex, but in others mainly affecting the outer or inner cell layers only. The changes were equally severe in the frontal, temporal, and occipital cortex, except in the calcarine region where the structure was better preserved. With high power examination the pale areas showed considerable loss of nerve-cells with characteristic advanced homogenizing degeneration in all those that remained. Even in the better preserved areas the majority of the nerve-cells showed a similar pathological alteration. The uniformity of this change in the residual nerve-cells was a striking feature in all the areas examined, but a few ischaemic cell lesions with incrustations were also seen. Throughout the cortex there was some degree of neuroglial and microglial proliferation. The blood-vessels showed some endothelial proliferation and thickening of their walls.

Summary of Case 6. A diabetic patient died after at least 36 hours' hypoglycaemic coma. Microscopical examination of the cerebral cortex showed widespread loss of nerve-cells, with severe homogenizing cell changes in the majority of the residual neurons.

Discussion

Comments on the pathological lesions. In discussing the pathological changes in the above six cases some general considerations should be borne in mind. In the first place the intensity and duration of the hypoglycaemia is not accurately known in respect of any of the cases. In Case 4 death took place three-quarters of an hour after the induction of coma, but in the others the patient survived in coma for different periods after the institution of adequate treatment, in Cases 2 and 5 for approximately 36 hours, in Case 3 for four days, and in Case 1 for 17 days. In Case 6 the time was uncertain,

but was at least 36 hours. Variation in the intensity of the pathological process and also in the resulting glial and mesodermal reaction is therefore to be expected. Again, in some of the cases previous attacks of hypoglycaemia with convulsions had occurred and it is possible that these attacks produced some permanent pathological changes. Furthermore, while in all the cases the nerve damage appeared sufficient to be the direct or indirect cause of death, it is probable that in Cases 4 and 5 cardiac failure was a contributing factor in the fatal outcome. If we examine our findings in this light it will be seen that the cortical changes in Cases 1, 3, and 6 are very similar, and differ only in the severity and stage of the pathological process. In these three cases a large part of the cerebral cortex had become necrotic with the disappearance of numerous nerve-cells. Although this necrosis often involved wide areas in their entirety, the frequently predominant involvement of the outer or inner layers (pseudolaminar necrosis) is especially to be noted. Irregular circumscribed lesions were infrequent apart from the selective damage of the Sommer sector in Cases 1 and 3 and the parastriatal region in Case 3, the latter contrasting strikingly with the well-preserved calcarine region. In these necrotic areas it appears that the nerve-cells which had disappeared had suffered irreparable damage with consequent rapid dissolution during the period of intense hypoglycaemia. Other cells not completely destroyed persisted and the pathological alterations found in these cells fall into three groups, namely, homogenizing, ischaemic, and severe cell change.

Special discussion of the homogenizing change is necessary, as the term seems to be used somewhat loosely in the literature, although it is a very characteristic alteration in the nerve-cells. Spielmeyer (1922) first used it to describe an alteration in the Purkinje cells, found in acute infections, where the cell body had become pale and opalescent or lightly stained, while the nucleus and the nuclear membrane had disintegrated round a very enlarged nucleolus. Husler and Spatz (1924) then used the term to describe cells found in necrotic areas of the cerebral cortex in which the cell body was not visible in Nissl preparations, but with eosin was stained faintly pink, the nucleus being deformed, triangular-shaped, and filled with darkly staining chromatin granules, some of which were concentrated round the margin of an enlarged and pale nucleolus. The term has come to be used according to Husler and Spatz's (1924) description, and the cell change is often stated to be closely related to the ischaemic cell change, from which it is nevertheless morphologically distinct. It may be justifiable to speak of early and late stages of homogenizing cell change. In Case 2 in the present paper there were numerous cells in the outer cortical layers in which the cell body was swollen and pale or vacuolated in Nissl preparations, while the nucleus was triangular and granular and the nucleolus invisible. We referred to these cells as showing an early stage of homogenizing change, but at the same time they are closely related to Nissl's severe cell change which, it is now recognized, can occur under similar pathological conditions. This homogenizing cell change was the most constant abnormality of the residual cortical cells in

these three cases, and it was the only characteristic change observed in Cases 1 and 6, whereas in Case 3 Nissl's severe change and the typical ischaemic cell change were also present. On the whole, examples of the latter abnormality were infrequent.

In Case 2, where few nerve-cells had disappeared, damage of all three types affected nearly every cell over wide areas. In Cases 4 and 5 intense cortical changes were found only in a few isolated foci, but elsewhere both cases showed widespread degeneration of the cortical nerve-cells, consisting mainly of chromatolysis and acute swelling, occasionally intermingled with severe nerve-cell change. It is possible but difficult to prove that the less severe and perhaps reversible cell changes in these two cases are to be correlated with the less intense and shorter hypoglycaemia which had lasted less than one hour in Case 4 and was partially interrupted in Case 5.

Although the cortical necrosis was slight in Case 4, the changes in the caudate nucleus and putamen were as severe as in any of the other cases. They must have been associated with previous comas, since the time available for their production during the fatal coma was too short. Indeed the severe affection of this region in four out of five cases (it was not available in Case 6) was a striking feature, and a contrast to the minor changes in the rest of the basal ganglia and the nuclei of the brain-stem and spinal cord. The relative sparing of the cerebellum too was noteworthy. A special feature in Cases 1 and 5 was a widespread glial fibrosis in the cerebral and cerebellar white matter and in the white matter of the brain-stem. It was not associated with an appreciable loss of myelin or axis cylinders and was also largely independent of the cellular degeneration.

Comparison with the pathological findings in the literature. The changes in our cases are similar to those previously described, and particularly allied to the detailed studies published by Stief and Tokay (1932 *a*, 1935), Bodechtel (1933), Leppien and Peters (1937), Cammermeyer (1938), Ferraro and Jervis (1939), and Winkelman and Moore (1940). Apart from the occasional occurrence of gross vascular lesions, the changes may be summarized as consisting of widespread disappearance and degeneration of nerve-cells in the cerebral cortex, basal ganglia, and cerebellum, with lesser affection of other nerve-cells throughout the nervous system. The focal and pseudolaminar necrosis of the cortex and the changes in the caudate nucleus and putamen are specially noteworthy and constant. Apart from the secondary glial and mesodermal proliferation in the grey matter, a widespread diffuse and perivascular gliosis of the white matter independent of degeneration and demyelination is sometimes found.

There is some disagreement in regard to the ubiquity of the nerve-cell changes. Winkelman and Moore (1940) concluded that every nerve-cell in the central nervous system might be affected, and they even described changes in the cells of the posterior root ganglia. Similarly Schereschewsky, Mogilnitsky, and Gorgaewa (1929) found changes in the sympathetic ganglia of the solar plexus. On the other hand some of the earlier workers (Ehrmann and Jakoby, 1924) have not mentioned nerve-cell changes, but it is not clear

what microscopic examinations they made, and others (Baker and Lufkin, 1937) have attributed them to post-mortem changes. As it is indeed difficult to distinguish the less severe nerve-cell changes from post-mortem alterations, care was taken in our investigations to draw conclusions only from nerve-cell changes of established pathological significance or when they formed part of a characteristic glio-mesodermal process of reaction and repair.

Before discussing the mechanism producing these pathological alterations, it is illuminating to compare them with similar changes occurring in vascular and anoxic conditions. In epilepsy, where cortical necrosis is considered to arise on a vascular basis, in status epilepticus (Scholz, 1933), and in pertussis eclampsia (Husler and Spatz, 1924), loss of nerve-cells and homogenizing changes identical with those occurring in hypoglycaemia have been found, although usually less widespread.

In strangulation similar changes are also found and Gamper and Stiefler's (1937) case showed the same degenerative processes as Case 2 in the present paper. Bodechtel (1928) described changes identical with severe hypoglycaemia in a man who died 14 hours after an operation during which the heart-beat ceased for 10 minutes, but where artificial respiration was continuous.

Several anoxic poisons produce similar effects, such as carbon monoxide (Meyer, 1928; Müller, 1930), cyanide (Meyer, 1933), and ether (Meyer and Blume, 1934), the last through respiratory failure.

Mechanism of the hypoglycaemic changes. Owing to the close similarity of the lesions in hypoglycaemia to those of vascular and anoxic conditions it is not surprising to find that the majority of workers have interpreted the changes on a vascular basis. A few workers have attributed the lesions to direct organic damage to the blood-vessels, such as endothelial proliferation. It is probable, however, that endothelial proliferation is part of the mesenchymal reaction secondary to the nerve-cell degeneration, which, as in Case 2 in the present paper, can take place without any involvement of the mesodermal tissue. In three of our cases vascular changes were inconspicuous. Most workers consider that transient vasomotor disturbances giving rise to pre-stasis and stasis are the main cause of the lesions (Bodechtel, 1933; Stief and Tokay, 1932*a*, 1935; Sahs and Alexander, 1939). Stief (1937) and Reitmann (1938) also suggested that insulin may have a vasoconstrictor effect on the blood-vessels. This would mean that temporary widespread ischaemia occurred in hypoglycaemia and gave rise to lesions identical with those produced in the conditions described above in which the oxygen supply or utilization is impaired. There is, however, no evidence that insulin has a direct effect upon the vasomotor regulation of the brain. Loman and Myerson (1936) and Ferris, Rosenbaum, Aring, Ryder, Roseman, and Hawkins (1941) found no significant alteration in the intracranial blood-flow during insulin coma. Leibel and Hall (1938) also found no changes in the blood-flow, unless convulsions occurred which considerably retarded the flow. The suggestion (Schmid, 1936) that an excessive output of adrenalin in response

to insulin may account for stasis and subsequent damage to the brain seems untenable, as adrenalin produces lesions greatly different from hypoglycaemia (Stief and Tokay, 1932 *b*). There is also no evidence of any direct effect of insulin on the brain tissue. If insulin is administered by intracerebral injections, hypoglycaemic symptoms occur only after a time necessary for absorption into the blood-stream, and the histological changes are not locally related to the place of the injection (Stief and Tokay, 1935). Dextrose given simultaneously with a large dose of insulin prevents any clinical or histological effect (Yannet, 1939). The only known constant and cardinal factor as regards insulin action on the brain is the reduction of blood-sugar.

The following considerations suggest that the removal of sugar from the brain might be expected to lead to similar and as profound lesions as the lack of oxygen in circulatory or general anoxic conditions. It has been proved that glucose is the main, and probably the only, substrate which the brain can use for its oxidative processes, so that the absence of glucose means a suspension of vital metabolism which, if prolonged, must lead to death and irreversible lesions in the nervous tissue. It should be pointed out that this lack of glucose is more complete than is often realized. Blood-sugar concentrations of 20 to 30 mg. per 100 c.c. are common findings in hypoglycaemic coma and, as the usual methods of estimation include about 20 mg. per 100 c.c. of reducing substances other than glucose, a reading of 20 mg. per 100 c.c. connotes a total absence of true sugar from the blood. Also, it has been proved experimentally, from the fact that the oxygen content of the jugular vein is abnormally high, whereas the saturation of the arterial blood is normal, that the oxygen utilization of the brain is reduced in hypoglycaemia (Dameshek, Myerson, and Stephenson, 1935; Himwich, Bowman, Wortis, and Fazekas, 1937). Obviously the term intracellular anoxia used by some workers refers to this non-utilization of oxygen by the cells in the absence of glucose. It is hardly correct to describe the hypoglycaemic mechanism as anoxia, since this term is reserved for the failure of the tissues to receive an adequate supply of oxygen and not for the absence of an oxidizable substrate. However, the practical results in disturbed functions and cell lesions are very similar and the terminological distinction a fine one. We suggest that the new word *oxyachrestia* would be useful and accurate (cf. achrestic anaemia, from χρῆσις = use).

Points of clinical similarity between the later stages of hypoglycaemia and anoxia have also been emphasized by Gellhorn, Ingraham, and Moldavsky (1938) and Fraser and Reitmann (1939). Clinical experience also suggests that the duration of hypoglycaemia is an important factor in determining whether or not permanent changes occur. In diabetics insulin coma is frequently followed by temporary mental and neurological changes, such as hemiplegia, but recovery is usually complete if treatment is prompt, however low the initial glycaemia. It is impossible to state from clinical experience the length of time required to produce irreversible or fatal changes, as the exact duration of coma is often vague, and the brain cells of different

individuals probably vary in their ability to recover from an attack. Experience suggests that coma of one to three hours is usually associated with complete recovery, while longer periods are dangerous. The use of slowly acting protamine insulin has increased the frequency of prolonged hypoglycaemia in diabetes and so the incidence of serious sequelae. The cases here recorded emphasize the desirability of abolishing the coma as soon as possible.

It is probable that, as in most severe anoxic conditions, vasomotor disturbances also arise. Another source of vasomotor disturbances is epileptiform convulsions. Vasomotor disturbances tend to aggravate the non-utilization of oxygen resulting from the absence of substrate. They may be held largely responsible for the gross haemorrhages and softenings which have been reported in a number of cases. The transient hemiplegias too, so commonly found after hypoglycaemia, are most easily explained on a vasomotor basis. It is, however, impossible to draw a sharp line of separation between the effects produced by general non-utilization of oxygen and vasomotor disturbances.

It has been suggested that epileptic convulsions are alone responsible for the lesions in the brain. In most cases of fatal hypoglycaemia fits are observed and it has been stated by Stief and Tokay (1932 *a*), Grayzel (1934), and Tani (1935), that severe histological lesions in the brains of experimental animals occur only after epileptic convulsions, but there is no strict parallelism between the frequency and severity of the epileptic phenomena and the severity of the lesions (Weil, Liebert, and Heilbrunn, 1938). In our material, too, the lesions in the brain were of a similar degree in Cases 1 and 3, although the former had no epileptic convulsions; also Case 2 had no fits, while in Case 4, with a number of severe fits, the histological changes were slight. Epileptic convulsions are now regarded as indicating a dangerous depth of hypoglycaemic coma and it is therefore not surprising that they are frequently observed in fatal cases with severe lesions in the brain. Convulsions in adult epileptics are, however, much less harmful to the brain tissue than is hypoglycaemia. Therefore, whatever the aggravating effect of hypoglycaemic convulsions may be, they do not exclusively account for the production of the histological lesions in the brain. It is interesting to note in this connexion, that in hypoglycaemia in animals convulsions are precipitated by simultaneous artificial anoxia (Gellhorn, Ingraham, and Moldavsky, 1938).

A few remarks are necessary about the interpretation of the glial fibrosis which appears to be independent of the degenerative process. This type of glial fibrosis without demyelination is not specific to hypoglycaemia, it has also been described in epilepsy, in cases of unknown aetiology (Bodechtel and Guttman, 1932), and in mental defectives (Meyer and Cook, 1937). MacKeith and Meyer (1939) in their example of insulin hypoglycaemia tentatively regarded it as a result of irritation of the glia by non-utilization of oxygen, and compared it with the fibrosis of other organs after mild stasis.

While the essential mechanism outlined above, namely the failure of vital oxidative processes in the absence of glucose and subsequent vasomotor changes, gives a satisfactory explanation of the main changes observed after irreversible coma, it is open to doubt whether it accounts for all the changes in the central nervous system and particularly those reversible ones in the earlier stages of uncomplicated hypoglycaemia. Yannet (1939) attaches great importance to disturbances of water metabolism, especially the shift of water from intracellular to extracellular spaces with loss of intracellular potassium, but Corwin (1939) was unable to alter the response of non-diabetic dogs to insulin by withdrawal of water for periods of from 24 hours to eight days. It would be tempting to associate with such changes the occurrence of oedema or dry swelling of the brain which has been reported, and also certain types of nerve-cell degeneration, such as acute swelling and the degeneration resembling water change. On the other hand it is impossible, on histological evidence alone, to rule out the possibility that these slight nerve-cell changes differ only in degree from the severe irreparable types of degeneration. Those experienced in the histology of anoxic conditions know that all types of nerve-cell degeneration occur together with the more specific cell changes. Our knowledge of the phenomena produced by hypoglycaemia and by anoxia is far from complete, and we have tried to confine ourselves to the comparatively few outstanding facts which can be safely interpreted.

Summary

1. The neuropathology of six fatal cases of hypoglycaemia is described in detail. The lesions were similar in all cases and differed only in the intensity and stage of the process. Widespread degeneration and necrosis of nerve-cells were found, with corresponding microglial and macroglial proliferation, and homogenizing and severe nerve-cell changes were the predominating types of degeneration. The cerebral cortex, the caudate nucleus, and putamen were most affected, the cerebellum less so, and the lesions in the remaining centres of the brain-stem were slight. In two cases a widespread glial fibrosis of the cerebral and cerebellar white matter was a striking feature.

2. The pathogenesis is discussed in relation to the biochemical alterations in hypoglycaemia and in comparison with similar lesions in anoxia. The main cause is considered to be the failure of vital oxidative processes from the lack of the substrate glucose, probably reinforced by subsequent vasomotor disturbances. The relative part played by the chemical and circulatory factors cannot be assessed and probably varies from case to case, but the primary factor seems to be chemical and akin to anoxia.

We are indebted to Dr. Lewis, Dr. Lilly, and Dr. Parfitt for clinical notes. We also wish to thank Mrs. E. Beck for technical assistance under a grant from the Rockefeller Foundation and Medical Research Council.

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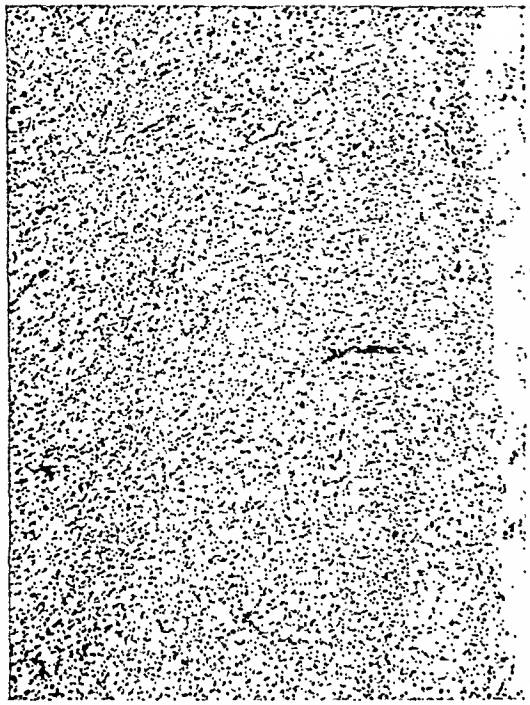

FIG. 1. (Case 1)

Complete degeneration of nerve-cells with intense new formation of neuroglial and microglial cells. (Frontal lobe. Nissl stain) (×55)

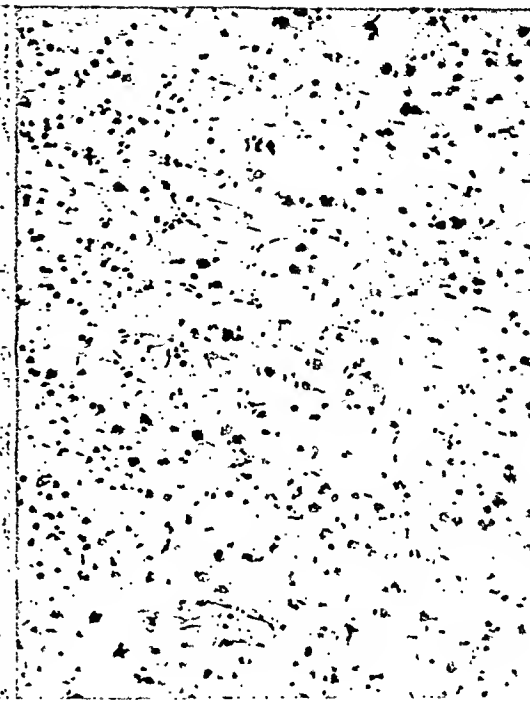

FIG. 2. (Case 1)

A less severely affected area of frontal cortex. (Nissl stain) (×140)

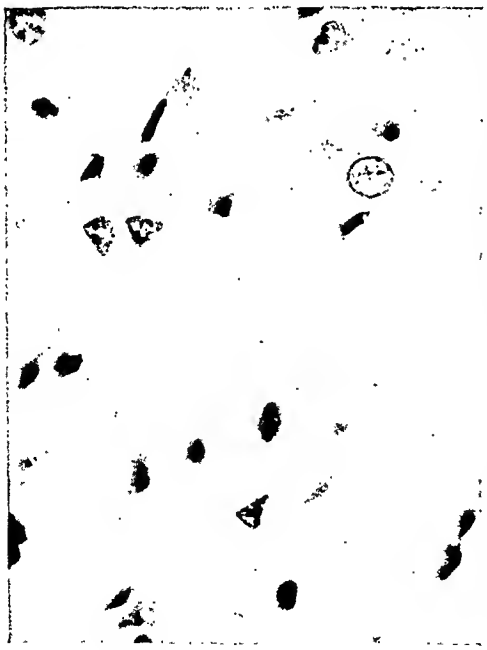

FIG. 3. (Case 1)

Showing examples of homogenizing cell change in the cerebral cortex (Island of Reil). Only the triangular-shaped nuclei are visible in the Nissl stain. (×700)

FIG. 4. (Case 1)

Microglial proliferation in the frontal cortex. (Kanzler stain) (×110)

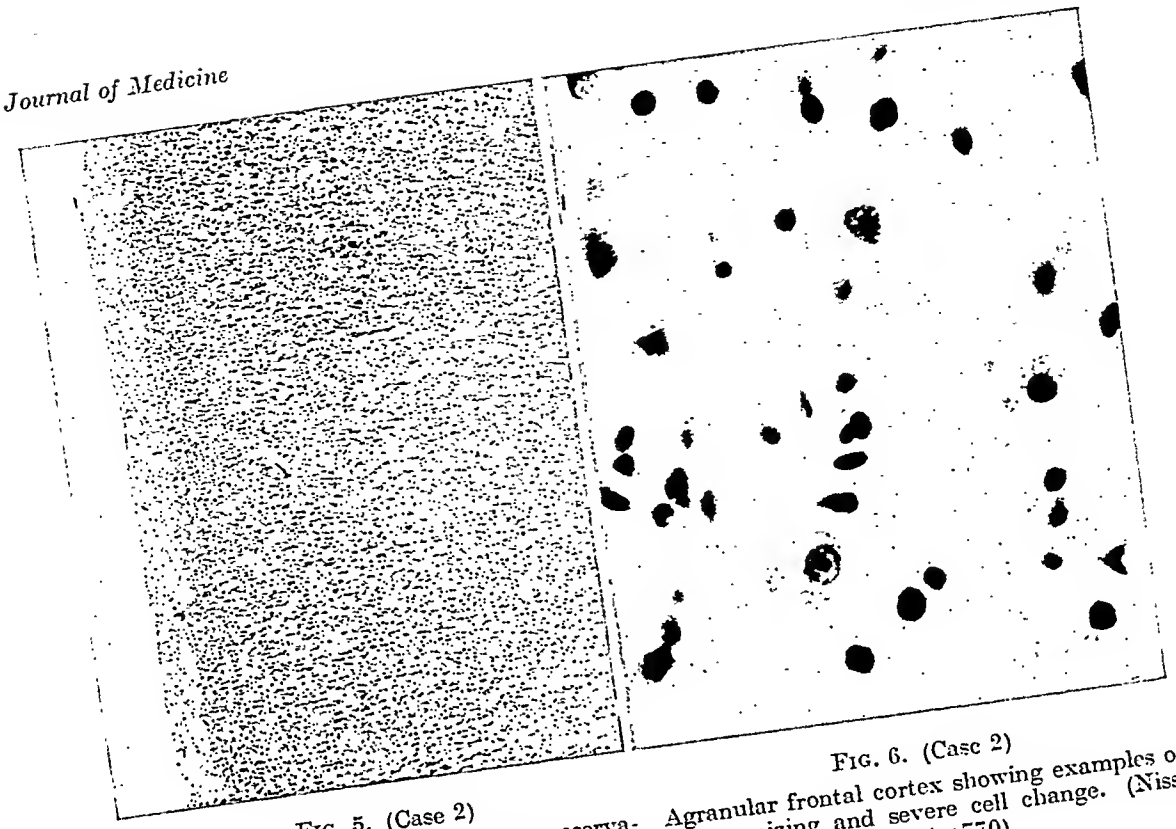

FIG. 5. (Case 2)
Agranular frontal cortex showing preservation of general structure. Under high power the nerve-cells show pathological alterations and there is a small area of pallor in the deeper layers. (Nissl stain) (×25)

FIG. 6. (Case 2)
Agranular frontal cortex showing examples of homogenizing and severe cell change. (Nissl stain) (×770)

FIG. 7. (Case 3)
Frontal cortex showing extensive pallor of the upper cortical layers, most severe in the depth of the suleus. On the right side a garland-like appearance has resulted. (Nissl) stain (×7·5)

FIG. 8. (Case 3)
High-power view of typical homogenizing cell change in a Nissl preparation of the temporal region. The nucleus only is seen with the enlarged and on the right side excentric nucleolus. (× 1250)

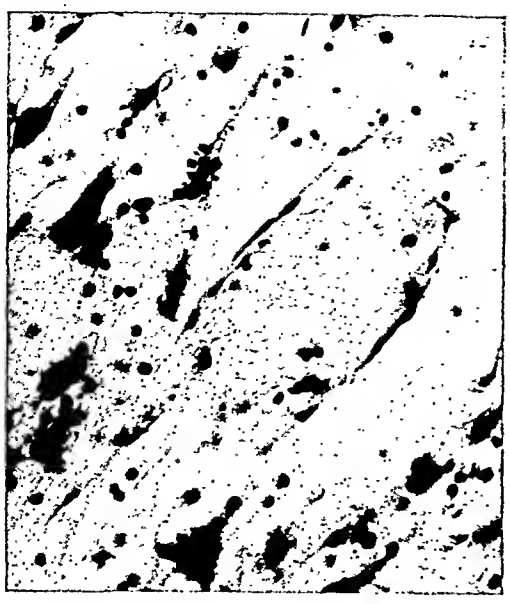

FIG. 9. (Case 3)
Ischaemic cell degeneration in the endfolium of Ammon's horn. (Nissl stain) (×600)

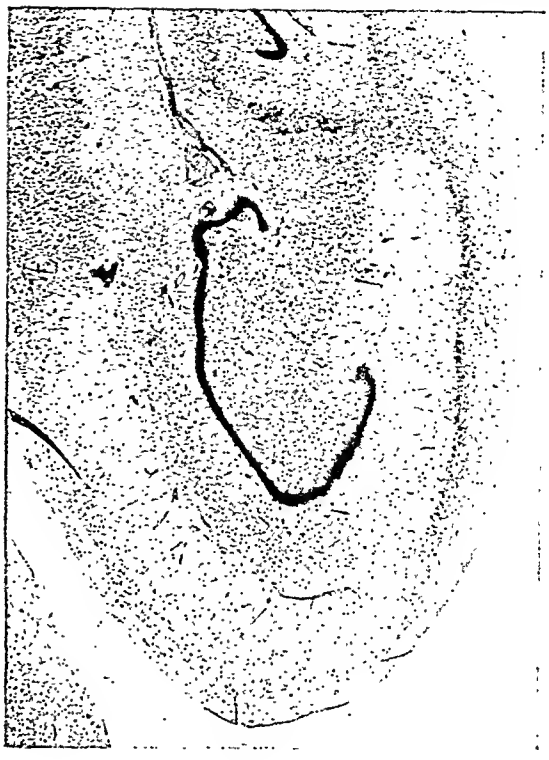

FIG. 10. (Case 3)
Showing typical destruction of nerve-cells in the Sommer sector and inner part of the endfolium of Ammon's horn. (Nissl stain) (×6·5)

FIG. 11. (Case 3)
Showing the pallor of the larger part of the putamen in a Nissl preparation. Only the most ventral corner has stained approximately normally. Note also the pallor of the insular cortex. (×1·5)

FIG. 12. (Case 4)
Temporal region showing cell alteration very similar to that known as water change, except for the chromatolysis of the marginal cytoplasm. (×600)

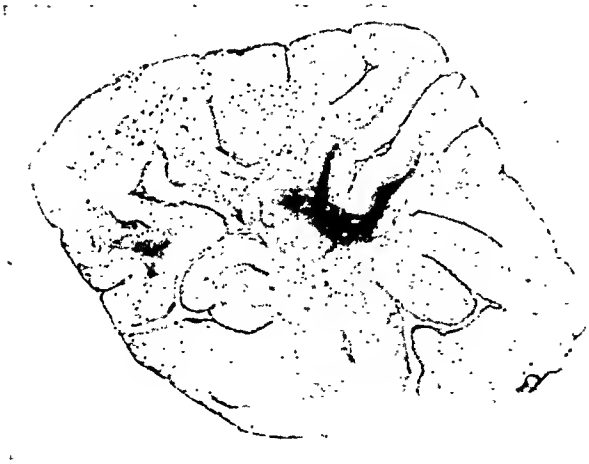

FIG. 13. (Case 5)
Showing the diffuse gliosis in the white matter. (Holzer stain) (×1·5)

616.71–018.3 . 616–006.31

MAFFUCCI'S SYNDROME[1]

(DYSCHONDROPLASIA WITH HAEMANGEIOMATA)

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With Plates 14 to 19

Introduction

The study of rare disorders has a scientific justification in addition to that of giving aesthetic pleasure to the clinical collector. As Garrod (1928) showed, such diseases may throw light on problems of normal physiology or give clues to the processes of determinative embryology and genic control. In the latter group are a large number of complex morphological anomalies which have been grouped together as germ layer dysplasias. They are all congenital, though symptoms may not present themselves until adult life; in certain instances they are clearly inherited, but in others there is no satisfactory information on this point. Thus neurofibromatosis (von Recklinghausen) may be described as a neuro-ectodermal defect and Lobstein's syndrome (fragilitas ossium, blue sclerotics, and ligamentary hyperflexibility) as a mesodermic dysplasia. In some examples the anomaly is limited to a single tissue, in others such as epiloia and Lindau's syndrome, the defects occur in tissues derived from several germ layers.

The morphological anomaly dealt with in the present paper is the association of defects in cartilage bone formation, dyschondroplasia, with vascular hamartomata, and it may be regarded as a mesodermic dysplasia. When morphological anomalies involve two distinct tissues, as in this syndrome, it is well to consider whether the abnormality in the one is determined by the other, or whether they are merely correlated. In Sturge-Weber's syndrome the cerebral agenesis is probably consequential on the vascular anomaly, and it is likely that the lenticular degeneration of Wilson's disease is secondary to the hepatic lesion. In conditions in which the endocrine glands are involved it is impossible to determine which is the controlling factor, but in Maffucci's syndrome, as in that of Lindau, it appears that the vascular anomaly is associated with, but does not determine, the other tissue abnormalities.

It is unnecessary to consider all the congenital abnormalities of the skeletal system. These have been admirably reviewed by Jansen (1928) and

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Fairbank (1934), but an account must be given of dyschondroplasia which is a component of Maffucci's syndrome and of diaphysial aclasis with which it is often confused. Dyschondroplasia, or Ollier's disease, is a condition affecting growing ends of bone in which the normal ossification of cartilage does not take place, and as the bone increases in length areas of cartilage which fail to ossify persist in the metaphysis. There is dwarfing of the affected limbs with irregular bending; the condition is commonly unilateral or markedly asymmetrical. The bones most frequently involved are the long bones of the arms, legs, hands, and feet. In the phalanges multiple enchondromata may occur with hideous deformity. There is little evidence of a familial tendency. Skiagrams show pale mottled areas in the metaphysis of the affected bones with thinning of the corticalis; there may be a uniform expansion of the metaphysis and speckling of the epiphysis. If exostoses occur they arise near the epiphysis, are irregular in shape, and point in any direction. Ollier (1900) demonstrated the bony changes in skiagrams only four years after Röntgen's discovery of X-rays, but it must be confessed that his description has caused confusion, for he failed to distinguish clearly between diaphysial aclasis and dyschondroplasia, as the latter term is now used by Hunter and Wiles (1934) and other critical authors, and laid undue emphasis on the one-sidedness of the condition. It is questionable whether multiple enchondromatosis, Jacobson's (1940) term for the condition, is preferable to dyschondroplasia, even though the latter term is liable to be confused with achondroplasia and Ehrenfried's (1915) ill-chosen 'chondrodysplasia'.

Diaphysial aclasis or hereditary multiple exostosis also affects cartilage bones at the growing end, but the misplaced cartilage is on the surface, not in the substance of the bone, and these areas of cartilage form exostoses (osteochondromata) which though they may appear anywhere along the shaft, most frequently occur at the growing end, and invariably point away from the end of the bone; they are clear-cut and often pedunculated. Synostoses may form between the radius and ulna and between the tibia and fibula. The metaphysis shows a sudden broadening and there is considerable irregularity of the epiphysis. Enchondromata may be present, but the ossification of the shaft is fairly uniform, and although there is commonly dwarfism, the curved deformities seen in dyschondroplasia are not found. In diaphysial aclasis the long bones of the hands and feet are not involved and there is no marked tendency to a one-sided distribution. The disorder is commonly familial; Stocks and Barrington (1925) in their extensive review found that in 1,102 recorded cases of diaphysial aclasis, 65 per cent. gave a history of the condition occurring in relatives. Ehrenfried (1915, 1917) made a study of diaphysial aclasis and suggested the unfortunate term hereditary deforming chondrodysplasia, which increased the confusion with dyschondroplasia. There is little doubt that Keith's (1919) term 'diaphysial aclasis' is preferable. Jacobson (1940), in an admirable review, brings forward morphological and genetic evidence to support the view that dyschondroplasia

(enehondromatosis) and diaphysial aelasis (multiple hereditary osteochondromatosis) should be regarded as distinet entities.

Maffucci's Syndrome

The first recognizable ease of the association of dyschondroplasia with haemangeiomata was described by Maffueei in 1881. Maffucci's syndrome is therefore suggested as an eponym for this disorder. Before Ollier's paper in 1900 the dysehondroplasia whieh he described and named was not elearly reeognized. It may have been referred to in earlier papers as eongenital riekets, and its existenee has often to be inferred from the history of fractures and deformities of the long bones. In a typieal ease, the ehild, generally male, is apparently normal at birth. During the years before puberty, any time from the first to the twelfth year, a hard nodule 1 to 2 em. in diameter appears, most eommonly on a finger or toe. This is soon followed by others, involving the extremities and the limbs. The distribution may be unilateral or extremely asymmetrieal. Dilated veins and soft bluish tumours occur in the affeeted limbs and elsewhere. Fraetures of one or more bones may follow a trivial injury, and union is slow and unsatisfactory. It may be noticed that development is uneven on the two sides. One or more of the long bones have short shafts, irregularly expanded ends, and cartilaginous tumours, especially near the epiphyseal line. One whole side of the ehild may remain dwarfed and deformed. The eurved uneven bones bring about secondary deformities, sueh as genu valgum, pes planus, ete. Though the eondition is very asymmetrieal, careful examination generally reveals that it is rarely absolutely unilateral. Throughout the period of development the deformities inerease. In severe cases the hands and feet bccome almost unreeognizable, and are transformed into huge masses of tumour growth, in whieh only the protrusion of a nail reveals the presence of a digit. The vertebrae, ribs, scapulae, and pelvis may all be the site of tumours. The skull, earpus, and tarsus, though not exempt, are rarely involved. In the early twenties, as growth draws to an end, the diseasc becomes stationary, but injury may eause exaeerbation of eartilage growth at any age, or even the appearance of further nodules. Malignant ehanges have been observed in a eertain number of eases. Affeeted persons are generally of low stature and poor muscular development. Intelligenee is average, and the internal organs appear normal. There is no pain. Mild cases of Maffucei's syndrome give rise to no disturbanee and are probably more eommon than the number of recorded cases would suggest. The ehondromata may mask the presence of angeiomata or *vice versa*, and a superficial clinical examination may miss the existence of more than one element. Routine skiagraphic examination of sueh eases is to be recommended.

Case Reports

Case 1 (Maffueci, 1881). *Bilateral dyschondroplasia and probable chondrosarcoma, with haemangeiomata.* The patient was a woman aged 40 years,

with four sons who were healthy. At birth a swelling was observed at the lower end of the left forearm, and about the third year tumours appeared on the left hand and slowly increased in size; the date of onset of the tumours elsewhere on the body is not recorded, but the tumours on the right hand were first noticed at the age of 17 years. Apart from the deformities she was a healthy woman of normal intelligence and came under observation owing to the inconvenience caused by a tumour on the left shoulder.

On examination she was short of stature and grossly deformed. In the right hand there was a large number of bluish tumours varying from 1 to 8 cm. in diameter, situated on the fingers and thumb; they varied in consistency, were compressible, and a few were tender on pressure. They appeared to lie in the subcutaneous tissues along the course of the veins; similar tumours were present around the elbow, and these had been observed to vary in size. The left arm was curved and shorter than the right. The hand was replaced by a nodular mass the size of a full-term foetal head and was formed of hard masses attached to the phalanges and metacarpals; there was also a nodule at the lower end of the radius. In the left scapulo-humeral region there was a nodular tumour 52 cm. in circumference occupying the whole of the acromial end of the clavicle, but not involving the joint. The skin was stretched over the tumour which had been increasing in size in the period previous to the patient's attendance at hospital. The right leg was greatly deformed by a large hard tumour in the intercondylar region of the femur, and the upper third of the tibia was sharply bent, consequent on a fracture in childhood; there were also small tumours on the phalanges and metatarsals. The left leg showed no abnormality save for a number of soft bluish tumours on the foot and ankle. Owing to the increasing size of the tumour in the left shoulder it was decided to amputate the arm and excise the tumour; this was done, but the patient died of pyaemia. At the post-mortem examination, in addition to the signs of pyaemia, it was found that the soft tumours were angeiomata, many of which contained phleboliths, and the harder tumours attached to the bones were chondromata; from the histological description it seems probable that the clavicular mass had undergone sarcomatous change.

Case 2 (Kast and von Recklinghausen, 1889). *Bilateral dyschondroplasia with haemangeiomata.* The patient was a small man aged 34 years (Plate 14, Fig. 1). When about six years old nodular swellings had been noted on the fingers of his right hand. At eight years there was a fracture of the left femur. At 10 years tumours appeared on the left hand and both feet, and from 16 to 22 years became larger and more numerous; from 22 years onwards the condition was stationary. His hands had meanwhile become transformed into 'tree-like' masses, measuring 30 cm. in length, and some of the fingers resembled cucumbers. There were also nodules around both knees and elbows, and on the spines of the scapulae, the vertebral column, and ribs. The skull was normal. Multiple angeiomata were present both in relation to bony nodules and elsewhere. There were patches of vitiligo on the trunk and limbs. As the man's hand was an encumbrance, it was amputated. It was then found that the bony tumours were enchondromata, that the angeiomata penetrated deeply between the muscles, and that a number of them contained phleboliths.

Case 3 (Steudel, 1892). *Bilateral dyschondroplasia with haemangeiomata.* The patient was a man aged 45 years (Plate 14, Figs. 2 and 3). Nodules had been noticed on the third and fourth fingers of his right hand at about

the age of six years; soon afterwards similar swellings appeared on the little finger of the left hand. The condition increased in severity, the bones being involved centripetally, the upper limbs being involved before the lower ones, and the right side before the left. At the age of seven years he suffered a fracture of the right tibia which healed normally, but the bone became curved; five years later this bone was again fractured, together with the left ulna and the left seventh and eighth ribs. By the age of 18 years the tumours had ceased to grow, but by this time he was grossly deformed and his right hand was of such a size that it could not be raised by the arm muscles. At the age of 20 years he was seen by Burk (1866) and amputation of the right forearm and left little finger performed. Burk described the case in a dissertation, and it was noted that the veins in relation to the chondromata in the amputation specimen were dilated and racemose, but no special comment was made on this, nor did Burk observe any angeiomata elsewhere in the body, though they were subsequently described by Steudel (1892). When aged 30 years the patient's nose began to enlarge and a swelling in the region of the right orbit caused a gradual protrusion of the eye, so that he was blind in this eye for the last seven years of his life. A year before his death there was severe pain after taking food, signs of portal obstruction, and an abdominal enlargement so gross that he became bedridden. Paracentesis was repeatedly performed, but he developed a terminal cystitis.

On post-mortem examination, in addition to the involvement of all the limbs, chondromata were found in relation to the right orbit and accessory air sinuses, and on the ribs and vertebrae, and there was a very large mass arising from the internal surface of the left iliac crest. Angeiomata were found throughout the subcutaneous tissue and in relation to the mesenteric veins, and it is mentioned that in some places there was a diffuse varicosity of the vessels rather than isolated tumour nodules. Firm nodules were present in the lungs, which were thought possibly to be secondary deposits, but there is no description of the microscopical appearances.

In Steudel's (1892) account it is stated that a brother of the patient died at the age of 12 years with similar tumours the size of cherries on two of his toes. This observation is of particular interest as it is the only example of a possible familial incidence, but the evidence for this is equivocal.

There is some bibliographical confusion with regard to the accounts of this case. In the first place the illustration (Plate 14, Fig. 3) in Steudel's (1892) paper (when the patient was aged 45 years) shows a young man with the right limb intact, but grossly deformed, even though it had been amputated 25 years before by von Bruns. Further, this lithograph is not identical with the illustration in Burk's (1866) dissertation (Plate 14, Fig. 2), although they clearly portray the same man. It seems probable that Steudel's artist copied the drawing in Burk's paper, but allowed himself some licence with regard to the face. The other point of confusion arises from the references in Stocks and Barrington's (1925) monograph. Burk's dissertation is referred to under No. 792 and a reproduction of the lithograph of the patient appears on Plate E, Fig. 2, but the dissertation is attributed to von Bruns and not Burk, though the title reads 'Inaugural-Dissertation zur Erlangung der Doctorwürde in der Medicin und Chirurgie unter dem Praesidium von Dr. Victor v. Bruns, ordentl. Professor der Chirurgie und Vorstand der Chirurgischen Klinik zu Tübingen, vorgelegt von Rudolph Burk aus Warmbronn'. In a letter from Dr. Stocks, who kindly lent us the only copy of Burk's dissertation known in this country, he says 'my recollection is that

Prof. Karl Pearson, who knew a good deal about the ways of German universities approved of this', namely, the attribution of the dissertation to von Bruns (who graduated in 1835) rather than to Burk who was in fact presenting it for the doctorate before the medical faculty of Tübingen University of which von Bruns was the presiding professor. Stocks and Barrington refer to Steudel's account under No. 826 of their Bibliography, and the pedigree is numbered 173 (p. 170). Here it is called Steudel and Burk's case, and it is mentioned that the patient was seen by Burk in 1866, but no cross reference is given to their bibliography No. 792 where Burk's dissertation is incorrectly attributed to von Bruns. It has been felt expedient to give this explanatory note as Stocks and Barrington's monograph is a *locus classicus*, and it is probable that future writers may be unable to refer to Burk's dissertation.

Case 4 (Nehrkorn, 1898). *Multiple bilateral chondromata and angeiomata with apparently unilateral dyschondroplasia.* The patient was a man aged 45 years. The deformity on the right side was first evident when he was three years old, and crippled him increasingly as he grew up. The musculature of the affected side was atrophic. The first nodule appeared on his right fifth finger at the age of three years, later his hands became completely deformed, and tumours involved the limbs and feet. Enlarged veins and angeiomata covered the forearms, hands, legs, and feet. As there was an increase in size of the tibial tumours, amputation of the right leg was performed above the knee. In a description of the specimen it is stated that the vascular tumours resembled telangeiectasia rather than angeiomata. His family history is described as being without significance.

Case 5 (von Kryger, 1898). *Unilateral dyschondroplasia with multiple bilateral chondromata and angeiomata.* The patient was a woman aged 54 years. Her symptoms began at the age of seven years, with cartilaginous tumours on the right hand and subsequent involvement of the left hand and right foot. Nodules about 2 cm. in diameter appeared on the heads of the metacarpals. The extremities became progressively deformed, with angeiomata in which little hard nodules were palpable, presumably phleboliths. The tumour mass in the right foot grew until it formed an oval mass about 20 cm. in diameter, and amputation was performed. The long bones of the right side were shorter than the left, and deformed. There was a subluxation of the right knee joint, with exostoses on the neighbouring bones. No mention is made of the family history.

Case 6 (Kirmission, 1900). *Angeiomata with a chondroma and probable dyschondroplasia.* The patient was a girl aged 14 years, with no significant family history, who developed at the age of fifteen months angeiomata of both feet and around the umbilicus, and deformities of both knees and ankles. At the age of five years, after a fairly severe injury, a tumour developed on the fifth finger of the left hand. When she was examined it was found that she had a considerable enchondroma of the proximal phalanx and some enchondromatous change in the metacarpal and intermedial phalanx of the fifth finger, which was amputated. The angeiomata, in addition to those around the umbilicus, were most marked on the right foot, where there was hypertrophy of the great toe; those on the left foot were less numerous and there were no gross deformities. The right knee was swollen owing to an enlargement of the femoral condyles and head of the tibia, there was some swelling of the right ankle, and there was a firm subcutaneous nodule

whose nature was not ascertained. On the left side there was little abnormality but for an enlargement of the head of the tibia; skiagrams are said to have been of no value. The question of congenital syphilis was considered and rejected. The illustrations show the deformity of the right knee, but there is no asymmetry. Although the evidence of dyschondroplasia is not complete, the appearances are highly suggestive.

Case 7 (Torri, 1902). *Bilateral angeiomata and enchondromata.* The patient was a woman aged 27 years, with nine siblings who were normal. She had not walked until the age of four years, and about this time a tumour the size of a pea appeared on the index finger of the right hand; shortly afterwards similar tumours appeared on the palm of the right hand and the left foot. At the age of 10 years the right arm became involved, at about 17 years a mass appeared in the right breast, and at the age of 20 years swellings appeared around the mouth and on the left hand. When she was 23 years old she had a fit, followed by a left hemiparesis and right oculomotor palsy; the hemiplegia gradually improved, but the oculomotor paralysis persisted, and she began to lose the vision of the right eye. On examination she was considerably deformed, with multiple angeiomata and chondromata on both hands, angeiomata on the right forearm, and a chondroma in the region of the left elbow. The left foot was oedematous with multiple angeiomata which were also present around the knee. There were angeiomata on the right cheek, lower lip, tongue, and soft palate. The chest was grossly deformed with chondromata on most of the left ribs, but none on the right, although there was an angeioma in the right breast. In spite of the deformities and aortic valvular disease she was in quite good health. Biopsies were performed to confirm the diagnosis.

Case 8 (Boinet and Stephan, 1903; Boinet, 1904). *Unilateral dyschondroplasia with multiple angeiomata and chondromata undergoing malignant changes.* The patient was a man aged 37 years. When about 12 years old he noticed small hard tumours on the fingers and dorsum of his right hand, which he attributed to having caught it in a door at the age of eight years. The long bones of both right limbs were shortened, atrophic, and deformed, with chondromata near the epiphyses. Traces of a healed supracondylar fracture were visible in the right femur on skiagraphy. He had numerous scattered angeiomata. Though the tumours ceased to grow at the age of 21 years, a fall on the right heel when he was 30 years old which caused a supramalleolar fracture of the tibia was followed some time later by a chondroma of the os calcis. This was curetted, but recurred 14 months later and proved to be malignant. His limb was amputated, but a malignant chondroma of the body of the sphenoid had already begun to manifest its presence, and he died shortly afterwards. At post-mortem it was found that the vascular tumours were both angeiomata and phlebectasic vessels. His family history is described as negative.

Case 9 (Thiemann, 1909, subsequently described by Weigeldt, 1925). *Bilateral dyschondroplasia with hirsute varicosities and vitiligo.* The patient was a man aged 37 years (Plate 14, Figs. 4 and 5). At a year old a nodule appeared on a finger of the right hand, and further nodules appeared on both hands and feet, the long bones, ribs, scapulae, and pelvis; the lesions were symmetrical in places, but the right side was more severely involved than the left. In addition there were angeiomata and considerable varicosities, many being hirsute; there was some hypertrophy of the hair and

nails of the hands and asymmetrical vitiligo on the abdomen and gluteal region. After an accident a tumour on the left femur enlarged rapidly and was thought to have undergone malignant change, but there is no later report of the case. The skiagrams are typical of dyschondroplasia.

Case 10 (Harbitz, 1916). *Unilateral dyschondroplasia and angeiomata.* The patient was a man aged 58 years. For as long as he could remember he had had a row of small tumours on the dorsum and inner side of the right foot, a smaller tumour with a warty surface on the right big toe, and a hard tumour on the right third and fourth toes. At the age of 56 years he noticed a small growth beneath the right lateral malleolus which increased to about 6 cm. in diameter and became painful. All the tumours were removed and examined. The masses on the foot and great toe were cavernous angeiomata, but those from the toes and heel were myxochondromata, and the latter recurred and became sarcomatous. There is no reference to the family history, and the case is not altogether satisfactory as the report is merely based on the histology of the excised tumours. However, the skiagram of the foot is quite typical of dyschondroplasia.

Case 11 (Fraenkel, 1925). *Bilateral dyschondroplasia and angeiomata.* The patient was a woman aged 32 years. She had first noticed a rounded swelling on the ring finger of the right hand at the age of 12 years; this enlarged to such an extent that it was amputated three years later as it interfered with her work. Further swellings, soft and bluish or red, appeared asymmetrically on the hands and wrists, and superficial to the insertion of the pectoralis major muscle. It was considered impossible to make a definite diagnosis on clinical grounds. Skiagraphic examination revealed that the superficial tumours were angeiomata containing phleboliths, but that there were also numerous chondromata of the fingers and metacarpals. This led to a systematic skiagraphic examination of the skeleton, when further chondromata were seen in the metacarpals and phalanges of the left foot, and in the distal ends of the left ulna and right radius. They had given rise to no subjective symptoms and had not been observed on clinical examination. In some places, where the bones were pressed on by neighbouring angeiomata, a hollowing due to pressure atrophy had resulted. The woman had married at 18 years and had had two normal children, and three who had died from causes not mentioned.

Case 12 (Hultén and Lovén, 1929). *Unilateral dyschondroplasia with bilateral angeiomata.* The patient was a man aged 27 years, of medium size and weak musculature. Before he was 10 years old painless nodules began to appear on his right side. Skiagrams showed that three ribs, the coracoid process of the scapula, the ilium, and the tibia were also affected on the same side. There were numerous angeiomata with phleboliths on both sides, but chiefly on the right. There is no mention of the family history.

Case 13 (Orator, 1933). *Bilateral dyschondroplasia with angeiomata.* The patient was a man (Plate 14, Fig. 6). Only a very brief and incomplete account of this case is available. The left hand was covered with chondromata and strongly resembles Kast and von Recklinghausen's (1889) case. The right side in a photograph appears deformed and stunted, and multiple angeiomata are visible. There is no reference to the family [illegible].

Case 14 (Casini, 1935). *Unilateral dy[illegible]oplasia wit[illegible]ngeiomata and pedunculated fibromata.* The [illegible] man age[illegible] Plate 14,

Fig. 7). Shortly after birth a small tumour appeared on the right thumb. A few months later further tumours developed, and during subsequent years involved the right hand and foot. At the age of 11 years he sustained a fracture of his right tibia in its lower third, and this healed slowly with subsequent curvature. About puberty the right hand began to enlarge and formed an enormous mass so that he was unable to work. At the age of 25 years there was cessation of growth of the nodules. By then the right foot had also become involved. Numerous angeiomata were found on both sides, but especially the right. The skin over them was mobile, and the tumours elastic, compressible, and bluish in tint. Skiagraphic examination revealed changes in the long bones of the arm and leg, third rib, and ilium on the right side. There were also pedunculated tumours, probably fibromata, of soft elastic consistency on the umbilicus, prepuce, and right side of the trunk. No abnormality was found in the urine, blood-count, blood-calcium, or blood-coagulation time. The Wassermann reaction was negative. Tests with adrenalin, pilocarpin, and atropin showed a 'slight parasympathetic tonus'. The right hand was amputated and weighed 4 kg. There were multiple cavernous angeiomata and myxochondromata. The tumour from the umbilicus was also examined and described as a fibroma, but the photomierograph shows it to be an angeiofibroma. The man's father and mother were normal. He was one of seven sons, of whom three were normal and three had died of unknown causes.

Case 15 (Hellner, 1936). *Multiple bilateral chondromata and haemangeiomata with unilateral dyschondroplasia.* The patient was a man aged 40 years (Plate 14, Fig. 8). The disease began at about the age of seven years with the appearance of three small hard nodules on the fingers of the right hand. The whole hand gradually became involved. On examination he showed stunting and deformity of both right limbs, especially the upper. The whole of the right hand including the carpus was affected by chondromata and angeiomata, and the index finger of his left hand was similarly deformed. Skiagraphic examination showed that the bony changes were, with the exception of the left index finger, entirely on the right side, and there were numerous deep-seated angeiomata with phleboliths. There was no known deformity in his living kin, which included father and mother, one grandfather, one grandmother, and three sibs of which one was a brother with seven children, and another a sister with four. The right hand was amputated and showed multiple chondromata and cavernous haemangeiomata.

Case 16 (Laplume, 1936). *Unilateral dyschondroplasia and angeiomata.* The patient was a youth aged 17 years. At the age of four years he fractured the neck of the right femur which united normally, but this was followed by fractures of the lower end of the femur and right ankle with consequent deformities. On examination he showed a sublingual angeioma, the right arm was shortened owing to an abnormality of the humerus, and the hand was covered with tuberous angeiomata. The right leg was 20 cm. shorter than the left, with gross curvatures of the femur and tibia; the foot was small, deformed, and covered with angeiomata. The left side presented no gross abnormality. This case was described by the author as one of osseous angeiomata, but the skiagrams are clearly those of dyschondroplasic bones.

Case 17 (Riveros, 1937). *Unilateral dyschondroplasia and angeiomata.* The patient was a man aged 25 years (Plate 14, Fig. 9). The condition was heralded at the age of five years by the appearance of tumours on the left

thumb. Further nodules appeared on the left arm and leg, and the left side of the trunk. As he grew it became evident that the whole of the left side below the head was lagging in skeletal growth and muscular development. The affected side was covered by capillary and cavernous angeiomata, some with thromboses and many calcified. Examination by skiagram revealed further deep-seated tumours. Biopsies confirmed the skiagraphic appearances. There is no reference to the family history.

Case 18 (Zikeev, 1937). *Bilateral chondromata, dyschondroplasia, and angeiomata.* The patient was a boy aged eight years (Plate 14, Fig. 10). At three years it was noticed that his right leg was smaller and shorter than the left, and at four years subcutaneous nodules appeared, many being in relation to veins. Skiagraphic examination showed that on the left side, which clinically appeared normal, there were rarefactions of the fingers, foot, and pelvis. Multiple angeiomata existed, especially on the left side. His parents and sibs were reported as being perfectly healthy.

Authors' Cases

Case 19.[2] The patient was a woman aged 32 years of medium height with brown hair and hazel eyes. She came to the Radcliffe Infirmary on account of her little daughter, who had granuloma annulare. As the mother was exhibiting her child's lesions it was noticed that she herself had numerous tumours showing through the stocking on her left leg, and an oddly shaped right tibia. She was inclined to dismiss her own condition as unimportant, but on questioning gave the following history. The tibial deformity was first noticed in childhood. At the age of five years there was a fracture of the left humerus which united badly and slowly. Two hard masses appeared on her left index finger when she was 10 years old, and the finger was amputated at Newcastle, but was not examined histologically. At 16 or 17 years soft masses appeared on her left leg and foot. These had remained about the same in size and appearance, though sometimes one or two seemed to grow a little bigger.

On examination a diffuse enlargement of the right tibia was seen, affecting the lower 8 cm., chiefly on the antero-medial aspect. The swelling was tender on pressure, but otherwise caused no inconvenience. The left humerus was 4 cm. shorter than the right, and angulated about the middle of the shaft, so that the lower end projected forwards. A hard tumour could be felt at the distal end of the left in[illegible] carpal at the site of amputation. A small, hard, flat, mobile subcp[illegible]dule was present on the dor[illegible] of the right hand. In addition, sh[illegible]. 20 soft, lobulated, subepide[illegible] or subcutaneous angeiomata. Th[illegible] was not involved and th[illegible] looked normal save for the blue[illegible] underlying venous bl[illegible] palpation, the t[illegible] were s[illegible] and in places flaccid, they could l[illegible]ly evacuat[illegible] and the skin dim[illegible] them. They[illegible]ted on the[illegible]der surface of the toe, the sole [illegible]ot, the low[illegible]ect of the left leg (Figs. 11 and [illegible] side of [illegible] the front of the on the right [illegible]em. fre[illegible] No capillary was visible, [illegible]o murm[illegible]y of these [illegible]

[2] This case wa[illegible] R[illegible] on Nove[illegible] (Carleton and Rob[illegible]d it [illegible]Kast' be associated with t[illegible]th[illegible]r and was not known to [illegible]

many cases they were in close relationship to the superficial veins, which were unusually prominent. In size they varied from 0·5 to 2·5 cm. Except for the large tumour on the dorsum of the big toe they did not seem to be attached to the underlying fascia and were freely movable. Those on the sole were painful if the patient stood for long, but the remainder were painless. Her only complaint was that the tumours on the leg and foot 'oozed' so that her stocking stuck to them, and when it dried, stiff, whitish patches were left. This was found to be due to sharply localized but excessive sweating. When she was pregnant the vascular tumours became temporarily much enlarged. This is an observation of some interest, for it is recognized that certain angeiomata develop during pregnancy and may persist after delivery (Blum, 1931). In other respects the patient appeared a healthy woman. There was no evidence of any disease of the heart, lungs, abdomen, or nervous system. Her height was 157 cm. The long bones of the two sides, except for the fractured humerus, were equal in length. The nails were normal in appearance and not painful on pressure.

Family History. The patient was the only child of an irregular union, and no data were available about her antecedents except that she believed her mother to be normal. She herself was married and had three female children, aged 6, 5, and 1 years. The eldest child resembled her mother in hair and eye colouring, the second had fair hair and hazel eyes, and the baby had auburn hair and blue eyes. They were all examined skiagraphically, and none showed any bony abnormality. The eldest child suffered from granuloma annulare and showed signs of past tuberculous adenitis in the neck.

The patient was admitted to the Radcliffe Infirmary for investigation. The skin temperature was taken, and on one occasion it was found that the left foot and ankle were 1·5° C. cooler than the right, but at a later date when the room temperature was 22·4° C. the left instep was found to be 0·5° C. warmer than the right. Both legs were immersed in water at 16° C. for five minutes and then dried without rubbing. The return to normal temperature occurred at the same rate on both sides. Stabins, Thornton, and Scott (1937) have found that in glomic tumours the affected extremity regains heat more rapidly than its fellow, so that in 10 min. a difference of 6° to 8° C. may exist between them. It was noticed that when the bedclothes were removed the skin was dry, but in the course of a minute the tumours became covered with beads of sweat, which if wiped off were immediately succeeded by others. This sweating was never observed on either of the angeiomata above the knee. One c.c. of Doryl was injected subcutaneously. There was no apparent increase in general sweating and no subjective effects were felt; the local sweating was free as before.

Blood-pressure, R. arm, 120/70, L. arm, 118/70. Plasma-phosphatase (Jenner and Hay), 2·5 units (normal). Plasma-cholesterol (Bloor), 80 mg. per 100 c.c. (low). Blood-sugar, 100 mg. per 100 c.c. (normal). Blood-urea, 25 mg. per 100 c.c. (normal). Serum-calcium (Tisdal-Kramer), 11 mg. per 100 c.c. (normal). Wassermann reaction, negative. Meinicke reaction, negative. Urine, normal.

Skiagraphic examination. Skull, no evidence of chondromata or phleboliths. Spine, shoulder girdle, ribs, and pelvis, normal. Left humerus, the head and neck were normal, but there was chondromatous involvement of the middle of shaft with some calcification (Plate 15, Fig. 13). Left radius, there was slight broadening of the lower end with chondromatous areas (Plate 15, Fig. 15). Left hand, there were enchondromata in the metacarpals

of the thumb and index fingers and in the proximal phalanx of the thumb; the index finger had been amputated (Plate 15, Fig. 12). Left femur, normal. Right tibia, the upper two-thirds were normal, but the lower third was broadened with cortical irregularity and thickening; phleboliths were present and appeared to be eroding the cortex (Plate 16, Fig. 18). Right foot, normal. Left tibia, there was no broadening of the bone, but a little cortical thickening and irregularity on the anterior surface of the lower third; phleboliths could be seen in the soft tissues in relation to this area. Left foot, no deformity of the bones; there were phleboliths in the soft tissues of the dorsal and plantar surfaces, and a collection of phleboliths in the soft tissues on the outer surface of the proximal phalanx of the first toe (Plate 16, Figs. 16 and 17).

Histology. Nodule from anterior surface of left leg (R.I.S.H. 802/38). The sections show a normal epidermis; in the dermis are congeries of cavernous angeiomata which merge imperceptibly into phlebectasic vessels with greatly hypertrophied walls lying in the deeper layers of the dermis. The sweat glands are hyperplastic and irregularly arranged, and there is a curious myxomatous stroma surrounding the sweat glands and the larger blood-vessels (Plate 16, Fig. 19).

Nodule from sole of left foot (R.I.S.H. 862/38). This shows a typical cavernous angeioma, but there is some hyperplasia of the adjacent sweat glands.

Nodule from the back of the right hand (R.I.S.H. 967/38). This shows a typical cavernous angeioma.

Subperiosteal nodule from the right ankle (R.I.S.H. 967/38). This shows a cavernous angeioma with spherical thrombi partially occluding many of the blood-spaces; these thrombi show a varying degree of organization and many have undergone calcification, constituting in fact phleboliths (Plate 16, Fig. 20).

Bone from the lower end of the left radius (R.I.S.H. 967/38). This shows normal periosteum and compact bone of varying thickness, but at one point there is a break in the continuity, and there is an area of myxohyaline cartilage extending from the periosteum to the deeper layers of the cortex. At the edge of the cartilage there is some calcification and a sharp demarcation between the cartilage and the lamellar bone which is investing it. In the medulla there are normal lamellar trabeculae, but in addition a number of cartilaginous masses surrounded by lamellar bone. There are no vascular abnormalities in the area examined.

The case is, therefore, a mild example of Maffucci's syndrome, but it exhibits in the localized sweating and temperature changes some novel features. Localized sweating is seldom seen in simple haemangeiomata, but it is observed in certain cases of glomangeiomata, arteriovenous fistulae, and congenital phlebectasia. It is probable that certain of the vascular lesions in this case were in fact arteriovenous anastomoses, and the histology of the tumour removed from the front of the leg has some features reminiscent of the glomoid anastomosis.

It will suffice to recall that clinically a glomus tumour is a small, bluish or reddish nodule, usually single, and rarely bigger that 1 cm. in diameter. The hand is the most usual situation, especially beneath the nail, but the tumours have been observed in the limbs and shoulders. The outstanding feature is paroxysmal pain, spontaneous or evoked by the slightest of causes.

It sometimes clouds the patient's life to such an extent that amputation of the limb appears welcome and suicide a possibility. An occasional feature of these tumours is a change in the temperature of the affected limb, which is generally raised but may be lowered. This may be accompanied by sweating, restricted to the skin over the tumour or covering the affected limb. Sometimes the sweating may exist without any observed alteration in temperature. The cause of the sweating is obscure. The vascular dilatation alone cannot be the cause. In 22 cases of glomus tumour (Barré, 1922; Barré and Masson, 1924; Freudenthal, Anderson, and Weber, 1937; Greig, 1928; Kolodny, 1938; Mackay and Lendrum, 1936; Paulian, Popescu, and Marinesco-Slatina, 1933; Stout, 1935), only five showed sweating. It is interesting, however, that in the same 22 cases a rise of temperature was observed in only four, two of which showed extensive sweating of the hand or arm (Stout, 1935; Paulian, Popescu, and Marinesco-Slatina, 1933). Barré (1922) says of his case that in addition to the hyperthermia there were 'troubles sécrétoires'. Where sweating was unaccompanied by a rise in temperature (Stout, 1935; Kolodny, 1938), it was much more limited, in Stout's case to the finger, and in Kolodny's to the palmar surface of the affected phalanx. It is tempting to deduce from this that when, owing to the pathological state of the glomus, the local temperature reaches a certain height dispersal of heat is aided by local sweating.

De Witt Lewis (1930) collected 30 cases of arteriovenous fistulae. In two of these he noted hyperthermia with sweating, in two others sweating without change of temperature, and in two more hyperthermia without sweating, but this apparent lack of correlation between the two may depend on the moment at which the temperature was taken. When there is a local increase of heat the affected limb would at first give a higher reading than its fellow. When, owing to the excessive sweating, the temperature has been reduced, it may give a lower reading. This is suggested by the two different records in the present case, one higher, one lower than the unaffected limb. It would seem advisable in future cases to take the temperature on more than one occasion. In the glomus tumour, the fact that sweating is sometimes seen over the whole hand or limb suggests that, at any rate in these cases, a sympathetic reflex is at work, a suggestion supported by the occasional existence of Horner's syndrome in the same cases. Bickford (1937) has shown that a faradic stimulus will produce local sweating, and by a series of experiments he demonstrated that this was due to the direct stimulation of the sweat nerves in the skin. The impulses pass through the axons of a local sympathetic plexus.

Returning now to the case here recorded, it will be seen that it differs from the classical picture of a pathological glomus in that the tumours are multiple and painless instead of single and painful, but recalls it in the associated alterations of temperature and sweating. Multiple tumours have been recorded, though Freudenthal, Anderson, and Weber (1937) cast doubt on their authenticity, and pain, though the cardinal feature in a glomus

tumour, is sometimes slow to develop. For example, Wien, Perlstein, and Slepyan (1937) reported a case where the tumour, which had existed since childhood, became painful only after an injury at the age of 54 years. It is therefore possible that certain of the tumours are glomoid in nature, and the question arises, as Freudenthal, Anderson, and Weber (1937) have said, whether cells which resemble glomus cells are found not only in glomus tumours, but also in other tumours arising from vessel walls. In considering this possibility one may recall the 'multiple glomic tumours' which Bergstrand (1937) discovered actually within the tarsal bones, and the two small intramuscular growths 'comparable to glomic tumours' which Thomas (1933) found in the thigh of a young man, with accompanying hypothermia of the limb and excruciating pain on pressure. It appears that multiple tumours with many points of resemblance to glomic tumours, and with many or all of their symptoms, may be found in unusual situations. Whether they are true arteriovenous anastomoses of the glomic type it is not yet possible to decide.

Case 20.[3] *Dyschondroplasia with multiple haemangeiomata, terminated by the occurrence of a glioma of the brain.* An unmarried man aged 38 years was admitted to the National Hospital for Nervous Diseases in April 1939 complaining of headaches of increasing severity and vomiting which had been present for the previous three months. His past health had been remarkably good, and he had suffered from no illnesses except the deformities which will be described. His family history was uneventful; his father had died in middle life of asthma and his mother at an advanced age of senile decay. He had three brothers and three sisters all healthy. No instances of similar deformities could be traced in the family and there was no consanguinity between the parents.

For as long as he could remember his arms and legs had been deformed. The distortion of his limbs had been such as to prevent him from carrying out any occupation, but until recently he had been able to get about the house and garden. Throughout his life his hands, and to a less extent his feet, limbs, and trunk, had been the sites of numerous lumps and swellings, some very soft, others firmer. These had grown larger with the passage of time, and by their mechanical effect had increased the disability resulting from the bony deformities. Most of these subcutaneous masses were painless, but some were tender upon pressure, and about five years before admission the little finger of the left hand had been amputated on account of the size and discomfort of the large swelling which enveloped it.

Some four months before admission he had begun to suffer from paroxysmal frontal headaches of a throbbing character. These occurred especially on walking, increased in frequency and severity, and were accompanied by vomiting. The symptoms had confined him to bed after two months or so. He had also noticed a feeling of lassitude and deterioration of memory and concentration. More recently a progressive deterioration of vision had set in accompanied by intermittent diplopia. His hearing had not altered, but he was conscious of tinnitus in the right ear and of giddiness on first waking. There had been no weakness or sensory disturbances in his limbs and no fits

[3] This case was reported at a meeting of the Neurological Section of the Royal Society of Medicine under the title of 'A case of von Recklinghausen's disease with multiple bony tumours' (Elkington, 1938).

Skiagraphic examination. Skull, no evidence of chondromata or vascular calcification. Spine, the cervical spine was normal; the body of the twelfth thoracic vertebra showed compression of the left lower border and there was irregularity of the normal cancellous architecture in the upper left border of the first lumbar vertebra. There were multiple chondromata on the ribs on the left side (Plate 17, Fig. 22). Upper limbs, the right humerus was normal, but there were bodies resembling phleboliths in the soft tissues. The right radius showed a little cortical irregularity of the lower third of the ulnar border and foci of cortical destruction could be seen in the upper third of the ulna. There were phleboliths in the soft tissues of the wrist. In the right hand the carpus was normal, the metacarpals and phalanges showed cortical thickening with irregularities of the normal outline and spaces in the cancellous pattern, but there were no large enchondromata. There were very large numbers of phleboliths in the soft tissues (Plate 17, Fig. 21). The left humerus showed widening of the upper two-thirds of the shaft with irregularity of the cortical and cancellous pattern, and numerous areas of dense calcification. The left radius showed widening of the lower third of the shaft with cortical and cancellous irregularity and areas of dense calcification (Plate 17, Fig. 26). The carpus of the left hand was normal, but there were large enchondromata of the thumb and index finger and smaller ones in the ring finger. No phleboliths could be seen (Plate 17, Fig. 23). Pelvis, there were large chondromatous masses with calcification involving both ilia, but the pubes and ischia were almost normal (Plate 17, Fig. 25). Lower limbs, the head of the right femur was normal. There were enchondromata of the upper and lower third of the shaft although the middle was relatively normal. The left femur was similarly but more grossly deformed. The right tibia was broadened, with enchondromata of the upper and lower portions of the shaft and gross deformities of the extremities. The left tibia was similar, but the deformity was not so marked (Plate 17, Fig. 24). The tarsi of both feet were similar; the metacarpals and phalanges of both sides showed numerous enchondromata with more deformity on the left than on the right; no phleboliths were visible.

Ventriculography showed a very extensive filling defect in the body of the left ventricle with displacement of the ventricular system towards the right, which was interpreted as indicating an extensive tumour of the left hemisphere, probably gliomatous in nature.

A biopsy was performed on one of the subcutaneous nodules and it was reported that sections of the nodule showed a haemangeioma composed of a network of smaller and larger blood-vessels separated by thin layers of fibrous tissue, in some places fibroblastic, suggesting recent formation. The endothelial lining of the vessels was inconspicuous and no capillary channels were present. The tumour was therefore not a haemangioblastoma or capillary naevus. In places there were collections of lymphocytes.

Progress. In view of the patient's general condition and the probably malignant nature of the intracranial tumour it was decided that no form of surgical interference was justifiable. The patient gradually became weaker and died three months after admission to hospital.

A post-mortem examination was performed 20 hours after death. The body was very thin and the various deformities and subcutaneous tumours described in the clinical record were noted. The right humerus measured 34 cm., the left 30 cm.; the right forearm measured 28 cm., the left 25 cm.; the right femur measured 36 cm., the left 34 cm.; and the right tibia measured 29 cm., the left 28 cm.

Brain and spinal cord. On removing the dura mater a soft mass of tumour was found presenting on the inferior surfaee and outer lower margins of the left temporal lobe, about midway between the temporal and occipital poles. It was adherent to the dura over the postero-inferior part of the area where it eame to the surfaee. On seetion of the brain in the coronal plane the tumour was found to involve all the white matter of the temporal lobe, and on passing backwards the degenerated centre of the tumour extended inwards to 1 em. from the mid-line near the splenium of the corpus callosum whieh was involved in more diffuse growth. In its most posterior part it involved the lower and outer half of the occipital lobe. The greater part of what was obviously tumour substanee was neerotie, with a reddish indefinite margin of undegenerated tumour round it. The spinal eord was normal.

The lungs, heart, liver, kidneys, spleen, and suprarenals appeared normal. Numerous dark red tumours, varying in size from that of a pea to that of a broad bean, were present on the mesoeolon near its attaehment to the eolon. They were most numerous in its deseending and transverse parts (Plate 19, Fig. 37).

Histological examination. Apart from post-mortem autolytic ehanges whieh were eonsiderable, the kidneys, panereas, testes, and suprarenals were normal. The spleen and liver were passively congested, but no abnormality was deteeted. The eerebral glioma presented different histologieal appearanees in different situations. Where the living margin round the neerotie eentral portion lay in grey matter there was a narrow, extremely eellular zone, eomposed of eells whieh varied greatly in size. Many large eells with multiple nuelei, or masses of nuelear material round their periphery, were present, but the majority were small eells with darkly staining nuelei of varied size and shape, and an oval or ill-defined eell body. A few intranuelear inelusions were seen in eells of fairly large size. Mitoses were very numerous. No neuroglial fibres appeared to be formed by the tumour eells. Where the tumour invaded white matter it appeared as a diffuse increase of nuelei. These varied in size, from small elongated or oval nuelei of the same length as those of astroeytes, but narrower and eontaining more ehromatin, to large irregularly shaped nuelei or masses of nuelear material lying in large irregularly rounded eells. In these areas it was diffieult to make out the outlines of the smaller eells. Where the tumour was adherent to the dura mater it was broken up into irregular, alveolar eollections of eells by septa of eonneetive tissue. The blood-vessels were very numerous in the eellular areas, appearing as a elose network of small ehannels with well-formed eollagenous walls, and a slightly swollen endothelial layer. Through most of the degenerated area it was also possible to see the eollagenous outlines of vessels whieh here too were very numerous (Plate 19, Fig. 38).

The angeiomata varied from one another to some extent in their histologieal appearances, espeeially in the density and width of the septa which separated the blood-ehannels. In some, as in that removed during life, there were thin septa of eellular, fibroblastie tissue with relatively little eollagen. This was the ease in most of the tumours of the mesoeolon, and also in some of the subcutaneous tumours. In other tumours, especially those under the skin, the septa between the blood-ehannels were wider and were formed of dense, hyaline eollagenous tissue with an irregular admixture of elastie fibres. In some tumours septa of both charaeters were present. The endothelial lining of the blood-channels was everywhere thin and inconspieuous. No regular eoneentrie walls and no museular tissue could be seen round the ehannels exeept in some large vessels, on or near the edge of the tumours.

which represented the nutrient arteries and the veins. Small collections of lymphocytes or more diffuse infiltrations were seen here and there in the septa. A few channels were filled and completely obliterated by a dense mass of tissue formed of concentric layers with nuclei. The staining reactions of this indicated that it consisted of collagen with a few elastic fibres. This tissue appeared to have arisen from the organization of thrombi in the blood-channels.

Description of certain of the bones. The right femur (Plate 18, Fig. 30) measured 36·5 cm. from the tip of the greater trochanter to the distal part of the medial condyle, but a comparable length was difficult to determine owing to rotation and deformity of the condyles. The head and trochanter showed little external abnormality, although there was some erosion of the synovial cartilage on the under surface of the neck and a slight projection on the intertrochanteric line; there was also a nodular exaggeration of the tuberosity. The shaft appeared normal to a point 18 cm. distal to the greater trochanter, where there was a sudden concavity (possibly the result of fracture) and the distal half of the shaft and condyles appeared to be internally rotated through approximately 90°; it also appeared that the condyles had been abducted through 45°. The effect of these deformities was that the external condyle lay anteriorly and 4 cm. proximal to the internal condyle. Owing to the deformities it was impossible to draw any definite conclusions as to the shape of the distal portion of the shaft, but it appeared to be broadened, the popliteal plane had disappeared, and the epicondylar lines could not be identified. The condyles showed some erosion and nodularity. Cartilage extended over the lateral condyle, and there was some erosion of the patellar surface. On bisection it could be seen that for the most part there was a sharp demarcation between the compact and trabecular bone. The trabeculae were irregularly arranged and thickened, and there were scattered islands of cartilage in the medullary portion. The synovial cartilage of the head was normal and the trabecular pattern of the head and greater trochanter was essentially normal, but just below the greater trochanter there was an irregular area of cartilage, 5 × 2 cm., which was calcified only in a few points, extending from the cortex into the medulla. Just below the point of the shaft where rotation had occurred there was on the lateral (originally posterior) surface a zone of great irregularity of cortex, in places sclerotic, elsewhere greatly thinned and apparently replaced by cartilage, some of which showed calcification. There were scattered spherical collections of cartilage in the trabecular bone of both condyles and the condylar cartilage was normal, but there was an enchond[illegible] ·5 × 1·5 cm., arising in relation to the internal condyle. The red ma[illegible] ed to the upper sixth the shaft. The right tibia (Plate 1[illegible] measured 29 cm. from intercondyloid eminence to the inf[illegible] r surface. The shaft curved antero-posteriorly and the d[illegible] rotated internally thro 90° so that the internal malleolus [illegible]. The proximal showed little abn[illegible] of the c[illegible] re was an enchondr projecting poste[illegible] the latera[illegible] a convex protub below the medial[illegible] above [illegible] ion of the pop The head as a wh[illegible] d, there [illegible] tion of the tub and anterior erc[illegible] pro[illegible] i of origin c tibialis anterior. [illegible] from t[illegible] not abnc the distal extre[illegible] an[illegible] l ro[illegible] tuberances, althou[illegible] surfa[illegible] lleolus abnormal. On bisect[illegible] t[illegible] al [illegible]

articular cartilages were normal and there was the same irregular arrangement of the trabeculae as had been observed in the femur. Much of the medulla in relation to the lateral condyle was occupied by enchondromatous tissue which showed some calcification. There were also isolated nodules of cartilage in the shaft and these became more marked in the distal portion. One of the protuberances already described was bisected and seen to consist of a very thin layer of bone covering a zone of cartilage, 3·5 × 0·7 cm., merging laterally into thick, irregular, trabecular bone. On the periosteal surface of the tibia a number of phlebectasic vessels were observed, but there was no obvious abnormality of the nutrient vessels in either the femur or tibia, nor did the nodules of cartilage appear to be in close relationship to the course of these vessels in the medulla.

Histology. Sections were prepared from a large number of areas of the femur and tibia, and the following description is a synthesis of the changes observed (Plate 19, Figs. 31 to 36). The synovial cartilage is everywhere normal save for slight arthritic changes, and the cartilage cells are arranged in orderly columns (Plate 19, Figs. 31 and 32). The compact bone of the cortex is in places, particularly in the middle of the shafts, completely normal with well-patterned Haversian systems and a normal demarcation between fibrous periosteum and cortex; arising from the compact bone of the cortex are branching trabeculae of normal pattern. However, in the areas which appear most normal there are to be found islands of cartilage cells lying between Haversian systems (Plate 19, Fig. 33), and this persistence of cartilage becomes more marked in places, so that the appearance is that of a mass of hyaline cartilage surrounded at its edges by lamellar bone; in some zones the cartilage cells are arranged quite irregularly, elsewhere into spheres surrounded by fibrillary cartilage, and in some places the cartilage cells have a myxomatous stroma. In places the cartilage is undergoing calcification, but this does not appear to be related to ossification, and where there is an osseous covering to an enchondroma there is a sharp demarcation between the bone and cartilage (Plate 19, Fig. 35). In some of the convex protuberances observed in the tibia a direct transition is seen from fibrous periosteum to cartilage without the intervention of a layer of cortical bone, although there may be islands of bone within the cartilage mass (Plate 19, Fig. 34). The enchondromata all have a covering of well-organized lamellar bone, and there is an impression that these enchondromata correspond to bony trabeculae in which there has been a failure of complete replacement of cartilage by bone and a persistence of the growth of the cartilage (Plate 19, Fig. 36). A few of the cartilaginous islands show zones of myxomatous fibrous tissue within them. Nowhere are any abnormal blood-vessels observed within the medullary cavity, although a few phlebectasic vessels are present in the periosteum.

Chemical analysis of portions of bone and chondroma gave the following results:

	Chondroma	Bone
Calcium	21·3 %	20·0 %
Phosphorus	7·4 %	9·0 %
Phosphatase	58 units per 100 gm.	80 units per 100 gm.

Discussion

There are thus 18 recorded instances of the association of dyschondroplasia with vascular hamartomata, and two further cases have been described. Of these cases six occurred in female patients, 14 in male. In 11 the

dyschondroplasia was bilateral, in six unilateral, and the extent of its distribution was uncertain in three. In six of the cases in addition to the haemangeiomata there was an associated phlebectasia (this point is not referred to in the other cases), and in two there was vitiligo in addition. In 10 of the cases amputation was performed owing to the deformity of a limb, and in four definite sarcomatous change had occurred in the chondromata, and this was possibly true of three further cases. It may be that the incidence of chondrosarcomatous change (20 to 35 per cent.) is higher in Maffucci's syndrome than in dyschondroplasia alone, but no reliable figures are available as to the incidence of malignant change in cases unassociated with angeiomata, as the majority have been described during childhood. Post-mortem examinations have been carried out in only four instances. In addition to these typical examples of the syndrome there are four doubtful cases.

Case Reports of Doubtful Cases

Case 21 (Cruveilhier, 1835–42). In the atlas of pathological anatomy there is an illustration of an amputated left arm showing multiple angeiomata and phlebectasia, and many of the digits appear to show chondromata, but there is no clinical history and no mention of the presence of chondromata in the description of the specimen.

Case 22 (Hanssen, 1863). A man aged 60 years was admitted to hospital with a massive tumour of the left shoulder. Two years previously he had fallen on to this shoulder and for the previous year a tumour had been rapidly developing. During the clinical examination a subcutaneous angeioma was observed at the right wrist. The tumour was deemed inoperable and at post-mortem was found to be a chondroma (probably a chondrosarcoma). The right arm was injected and carefully dissected. It was found to show numerous cavernous angeiomata and phlebectasia of the superficial and deep veins, but there is no description of angeiomata or chondromata elsewhere, and the drawing of the arm reveals no deformities.

Case 23 (Harbitz, 1916). The patient was a youth aged 16 years who from early childhood had suffered from an increasing number of fibro-angeiomata on the left hand and forearm. The fingers on the affected side were smaller than on the other.

Case 24 (Halter, 1937). The patient was a youth aged 16 years who was born with a spiral of bluish red macules on the right side, extending from the gluteal region round to the front of the leg and to the dorsum of the foot. The macules developed into verrucous haemangeiomata and there was defective growth on the same side.

Apart from haemangeiomata, dyschondroplasia is sometimes associated with other anomalies. In Kast and von Recklinghausen's (1889) case and that of Thiemann (1909) there was an associated vitiligo, and this was also observed in a case of bilateral dyschondroplasia described by Boppé, Lièvre, and Franco (1934). Schweinberg (1907) described a case of bilateral dyschondroplasia with multiple pigmented naevi (melanomata) in a man aged 30 years. Hunter and Wiles (1934) noted that in six cases of unilateral dyschondroplasia (Bojesan, 1914; Johansson, 1916; Johannessen, 1923;

Bentzon, 1924; Jansen, 1925; Hessenthaler, 1929) there was a marked facial asymmetry. Multiple vascular anomalies are associated with other abnormalities in the syndromes of Lindau and Sturge-Weber. There is, too, the condition of multiple angeiomata with limb hypertrophy described by Gougerot and Filliol (1929) and Miescher and Burckhard (1938) as 'naevus variqueux ostéohypertrophique Klippel-Trenaunay'. In phlebarteriectasia and phlebectasia (Weber, 1918; Schmidt, 1926; Sonntag, 1928) there is also hypertrophy of the affected limb. Multiple angeiomata are not infrequently found in cases of multiple neurofibromatosis and have been described in association with spina bifida and multiple lipomata.

Pathogenesis

It would not be profitable to recapitulate the views on the formal genesis of vascular anomalies, which have been well summarized by Wertheim (1932), but it is necessary to consider the theories which have been propounded to explain the bone changes in dyschondroplasia in order to ascertain whether these may have any bearing on the vascular and pigmentary changes observed in Maffucci's syndrome.

Bentzon (1924), observing that the cartilaginous areas correspond with the distribution of the nutrient artery, suggested that they might be due to hyperaemia induced by anomalies in the sympathetic nervous system. Accordingly, he attempted to reproduce the changes in rabbits by destroying by alcohol injection the sympathetic fibres to the nutrient vessels. The results were unconvincing; many of the bones showed a marked periosteal reaction as the result of leakage of the alcohol. In two animals clear areas appeared in the bone on X-ray, and although it is claimed that these were cartilaginous masses, only one of the bones was examined histologically, and the appearances shown in photomicrographs are by no means characteristic. Jansen (1928) believed that the sympathetic system was at fault, but postulated a vasoconstriction rather than a vasodilatation.

Speiser (1925) made a most detailed morphological analysis of dyschondroplasia on the basis of a post-mortem on a four-year-old boy. He found pedunculated grape-like inward projections of cartilage from the epiphyseal plate and from the periosteal surface of the bone. In the older portions of the shaft typical enchondromata were present. He suggested that the abnormality results from a metaplastic activity of the periosteum and that the abnormality must commence some time between the fourth and eighth foetal months.

Jacobson (1940) favours the view that the morphogenesis is associated with failure of absorption of part of the cartilage growth plate of the epiphysis and that this may be induced by some abnormality of blood-supply or nervous control. This morphogenetic hypothesis is strongly supported by the examination of the bones in Case 20.

In view of the hypotheses of Bentzon (1924) and Jansen (1928), both involving a vascular change as the causal factor, the possibility of the

vascular anomalies inducing the bone lesions in Maffucci's syndrome must be considered. It seems that there is nothing to support this view. In the first instance, in many of the cases (this is well shown in Case 20 described in the present paper) though the lesions have been unilateral, yet the vascular changes have been most marked in the non-dyschondroplasic side, nor is there any close relation between the vascular and osseous changes in the homolateral cases. Further, in conditions associated with hyperaemia such as arteriovenous anastomosis, phlebarteriectasis, or phlebectasis, if there is a bony change it is one of uniform hypertrophy rather than irregular growth and atrophy. Jansen's view is not supported by the observation of known examples of sympathetic vasoconstriction such as the changes resulting from pressure on the sympathetic fibres of the arm by a cervical rib. Telford and Stopford (1930) have shown that in these cases the persistent arterial spasm results in narrowing and thrombosis of the vessels, but no bony changes have been observed.

However, it must be conceded that in most of these conditions the vascular change occurs in postnatal life and it is possible that an influence either vascular or nervous in the embryonic phase might induce profound bony change. Yet the evidence of the distribution of the vascular lesions in Maffucci's syndrome favours the idea that the anomalies are coincidental rather than consequential. There is some support for the suggestion that the changes, both vascular and bony, may be induced by a 'disseminated neurological lesion'. The striking tendency to onesidedness, the association in certain cases of facial asymmetry, vitiligo, or melanomata all suggest some neurotrophic factor. Further, in Case 19 the abnormalities of skin temperature and sweating are possibly of sympathetic origin. The possibility that this is the case is supported in an indirect manner by another curious bony condition, Albright's syndrome, in which there is a unilateral or asymmetrical fibrous dysplasia of the skeleton associated with skin pigmentation, endocrine gland disturbances, and skeletal precocity. In a certain number of cases of icterus neonatorum in which cerebral symptoms may arise as the result of kernicterus, the pigmentation and bony changes of Albright's syndrome have been observed to develop, and the hypothesis that the bony and pigmentary changes may be induced by degenerative changes in the neonatal brain is too attractive to be overlooked (Falconer and Cope, 1942).

It is probable that Maffucci's syndrome is a dysplasia arising at an early stage of foetal life, but the part played by inheritance is obscure. We have, in fact, little knowledge of the heredity even of the separate elements. It is doubtful whether cavernous angiomata are inherited or not, and the evidence from monozygous twins is too small to be conclusive either way. There is no doubt that certain cerebrovascular anomalies are inherited, probably as a dominant, but there is nothing to support an analogy between these conditions and dermic haemangeiomata.

A similar uncertainty applies to the inheritance of dyschondroplasia and multiple enchondromata. It has already been pointed out that confusion

has arisen because true cases of this condition have been grouped with diaphysial aclasia and intermediate states such as Voorhoeve (1924) described and regarded as being one and the same disease. It is now generally considered that there are at least two separate entities, and if this division be made there is little, if any, positive evidence of inheritance in dyschondroplasia and enchondromata, whereas there is no doubt whatsoever that diaphysial aclasis is very frequently inherited. When two abnormalities occur simultaneously in an individual the fact may be explained in various ways, such as:

(1) Accidental association; the laws of chance make this improbable.

(2) The multiple effects of a single gene.

(3) Linkage, i.e. the immediate proximity on a chromosome of two genes, each responsible for one of the abnormalities in question. A suggested example of linkage is the coexistence of ichthyosis simplex and a liability to asthma and Besnier's prurigo. Unfortunately for research purposes, most of the normal human characteristics are due to the action not of one, but of a number of genes. So that when pigmentation of the skin, for instance, occurs in two different syndromes, one cannot be sure that there is a common factor in each case.

(4) The co-operating or inhibiting action of other genes, serving either to heighten the effect of the main gene or to diminish, mask, or even alter its effect. The presence in the same chromosome of a second alternative gene would explain the tendency for a disease to take on a specially characteristic form in one family; as for example, one family group in which von Recklinghausen's disease is manifested always as elephantiasis neuromatosa, whereas in another pigmentary disturbances alone appear.

(5) The co-operation of a single gene and an environmental factor. In the blue sclerotic syndrome mentioned above, the scleral abnormality is due to an abnormal dominant gene, but the fragilitas ossium, according to Haldane (1938), is more probably caused by an environmental factor.

The most likely hypothesis is that these groups of associated abnormalities are due to the multiple effects of single genes, influenced by alterations in the environment, or in the rest of the gene complex, but it is obvious that the present state of knowledge is inadequate to solve the puzzle presented by these grouped defects. We can do little more than assemble the various pieces and hope that in the future they may fit together. Further light may be thrown on the problem by noting the appearance of the same or apparently the same defect in different groups. Laxity of ligaments, for instance, is found in the blue sclerotic group and also in the Ehlers-Danlos syndrome, characterized by articular hyperextensibility, especially of the thumb, by cutis elastica, and by undue fragility of the skin and its capillaries. The only evidence that Maffucci's syndrome may be an inherited abnormality is the report by Steudel (1892) of its doubtful occurrence in two brothers. In future cases it will be of special interest to discover whether there is a high percentage of parental consanguinity, a question which has

unfortunately been overlooked in the family histories available. With regard to the preponderance of males to females (14 to 6 in the collected cases), this departure from equality might appear to be significant, but applying Fisher's rule (Roberts, 1940) it is at once seen that it could easily have arisen by chance, and it cannot be assumed that it is due to sex linkage or is even sex-controlled.

Summary

1. A syndrome characterized by the association of dyschondroplasia (Ollier's disease) and vascular hamartomata (cavernous angeiomata and phlebectasia) is described, and it is suggested that it should be associated with the name of Maffucci who gave the first account of the condition in 1881.

2. Eighteen examples of the syndrome have been collected from the literature, and two further cases are added. There are four additional cases which may be 'formes frustes'.

3. One of the original cases was unusual in that the vascular hamartomata were associated with abnormalities of sweating, and the other died as a result of a cerebral glioma.

4. Analysis of the cases suggests that the two components of the syndrome have a coincidental association, and that the vascular anomalies do not induce the bone changes, but it is possible that they are both consequent on a foetal neurotrophic disturbance. Morphological examination of the bones supports the hypothesis that dyschondroplasia results from a failure of absorption of the cartilaginous growth plate of the epiphysis. There is no evidence to uphold the view that the syndrome is inherited. It probably belongs to the group of congenital mesodermic dysplasias.

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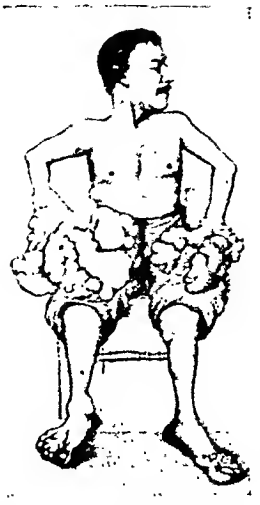


FIG. 1. Case 2. (Kast and von Recklinghausen, 1889)

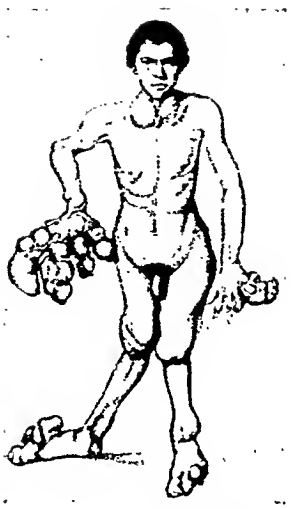


FIG. 2. Case 3. (Burk, 1866. Illustration when the patient was aged 20 years)

FIG. 3. Case 3. (Steudel, 1891. Illustration when the patient was aged 45 years)

FIG. 4. Case 9. (Thiemann, 1909. Illustration when the patient was aged 19 years)

FIG. 5. Case 9. (Weigeldt, 1925. Illustration when the patient was aged 37 years)

FIG. 6. Case 13. (Orator, 1933)

FIG. 7. Case 14. (Casini, 1935)

FIG. 8. Case 15. (Hellner, 1936)

FIG. 9. Case 17. (Rivarus, 1937)

FIG. 10. Case 18 (Zakrzewski, 1937)

FIG. 11. Case 19. Photograph of left ankle showing the angeiomata and deformities

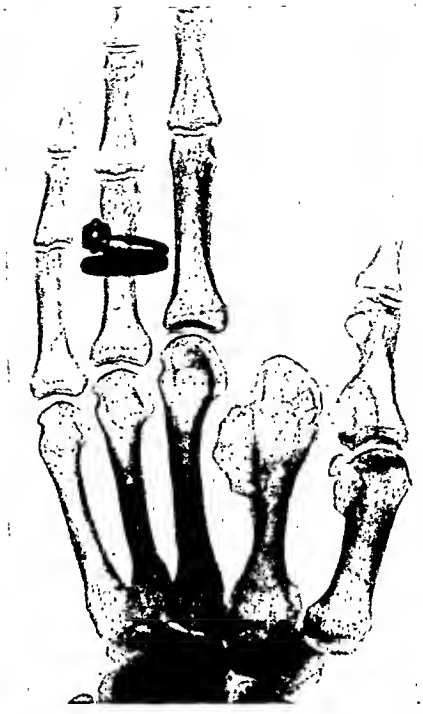


FIG. 12. Case 19. Skiagraph of left hand showing enchondromata

FIG. 13. Case 19. Skiagraph of left humerus showing broadening and deformity of the shaft with rarefied areas (chondromata)

FIG. 14. Case 19. Photograph of left ankle showing the angeiomata and deformities

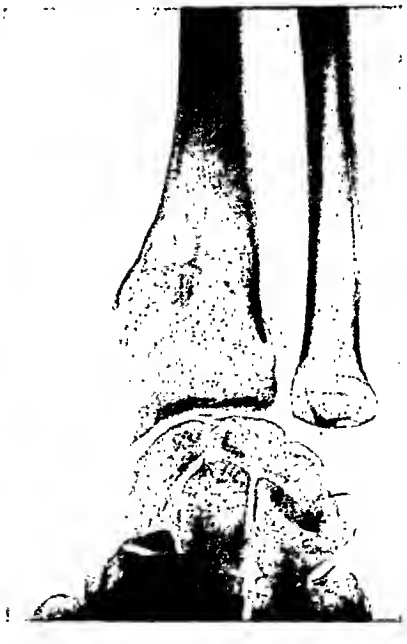


FIG. 15. Case 19. Skiagraph of left radius showing broadening of the lower end with chondromata

FIG. 16. Case 19. Skiagraph of left foot showing irregularity of the anterior surface of the tibia and tarsal bones, together with numerous phleboliths

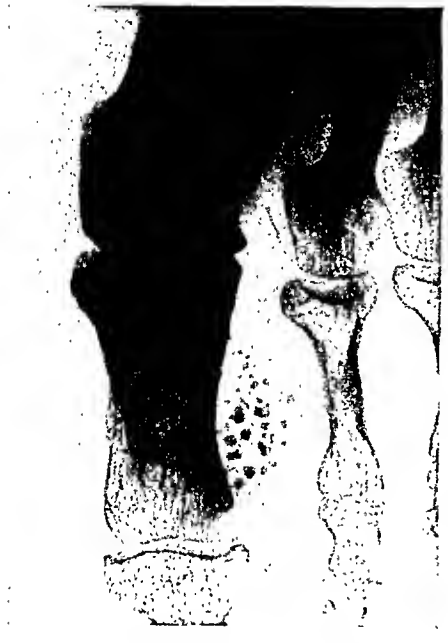


FIG. 17. Case 19. Skiagraph of left great toe showing phleboliths

FIG. 18. Case 19. Skiagraph of right ankle showing cortical irregularity and phleboliths on the anterior surface of the tibia

FIG. 19. Case 19. Photomicrograph of nodule from the left ankle showing cavernous angeiomata and phlebectasic vessels (haematoxylin and eosin. × 85)

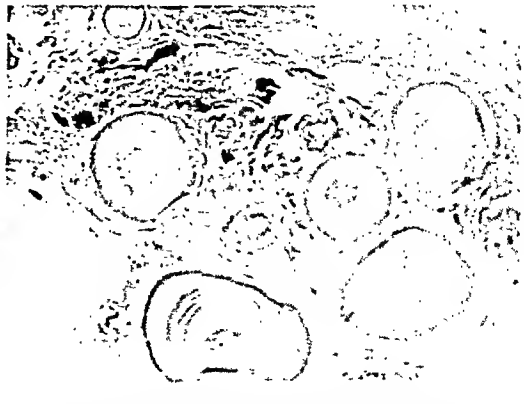
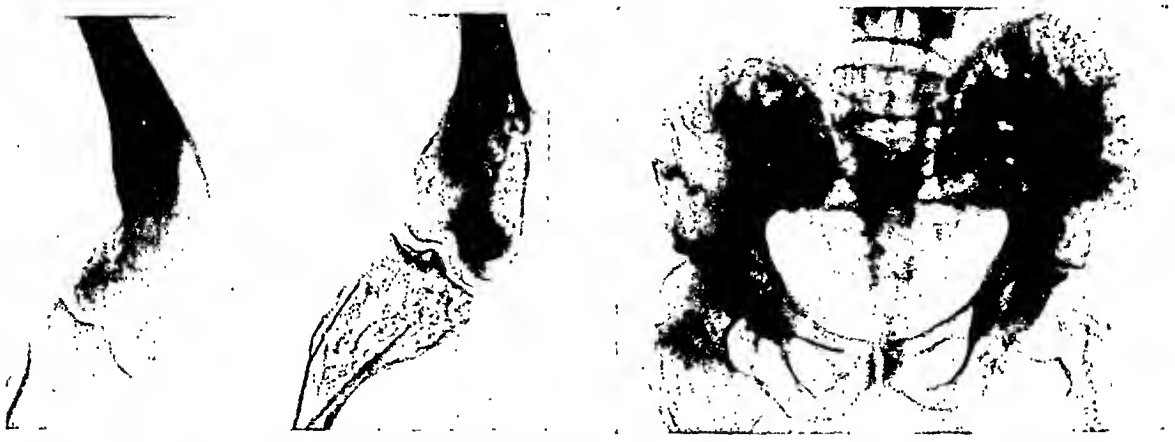
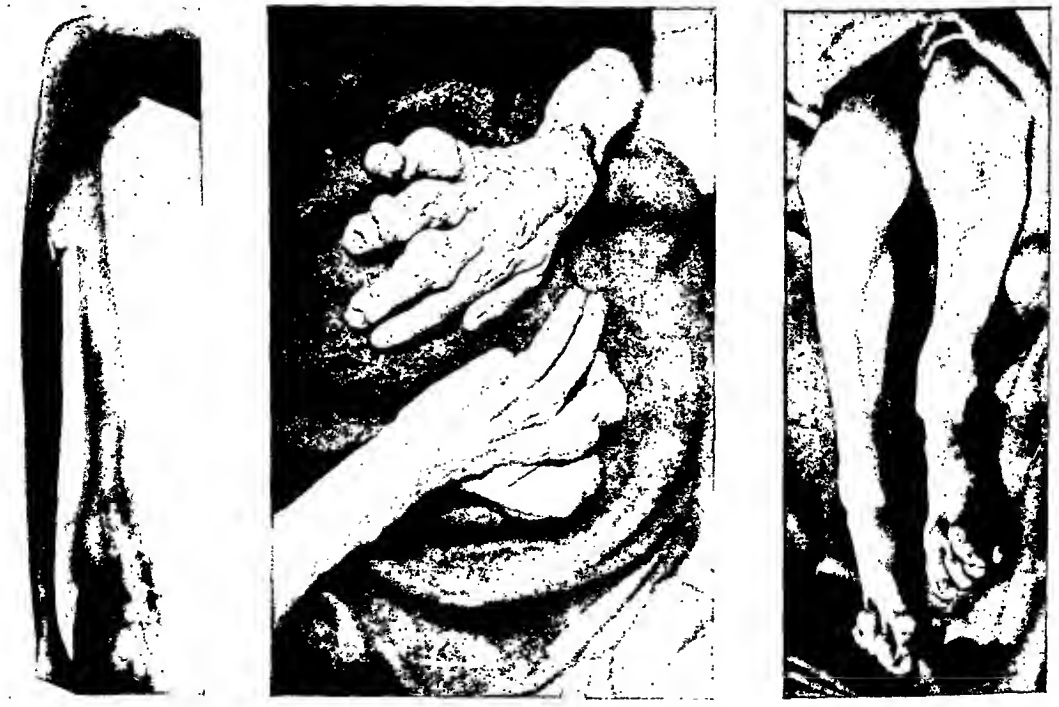


FIG. 20. Case 19. Photomicrograph of subcutaneous nodule from the right ankle showing a cavernous angeioma with phleboliths (haematoxylin and eosin. × 12)

FIGS. 21–3. 21. Case 20. Right hand showing deformities and areas of calcification of the metacarpals and phalanges together with large numbers of phleboliths in the subcutaneous tissues. 22. Case 20. Chest showing chondromata on the left ribs. 23. Case 20. Left hand showing the chondromata and deformities of the metacarpals and phalanges, but a complete absence of phleboliths



FIGS. 24–5. 24. Case 20. Both knees showing the deformities and irregularities in the lower ends of the femora and the upper ends of the tibiae. The changes in the bony structure are more marked on the right than on the left. 25. Case 20. Pelvis showing the chondromatosis of the ilia and the deformities of the femoral heads



FIGS. 26–8. 26. Case 20. Left forearm showing deformity and broadening with decalcification of the lower end of the radius. 27. Case 20. Showing deformities of the hands resulting from chondromata and angeiomata. 28. Case 20. Showing the shortening of the left leg with deformities of the tibia and fibula at their upper and lower ends. The angeiomata on the toes can be seen

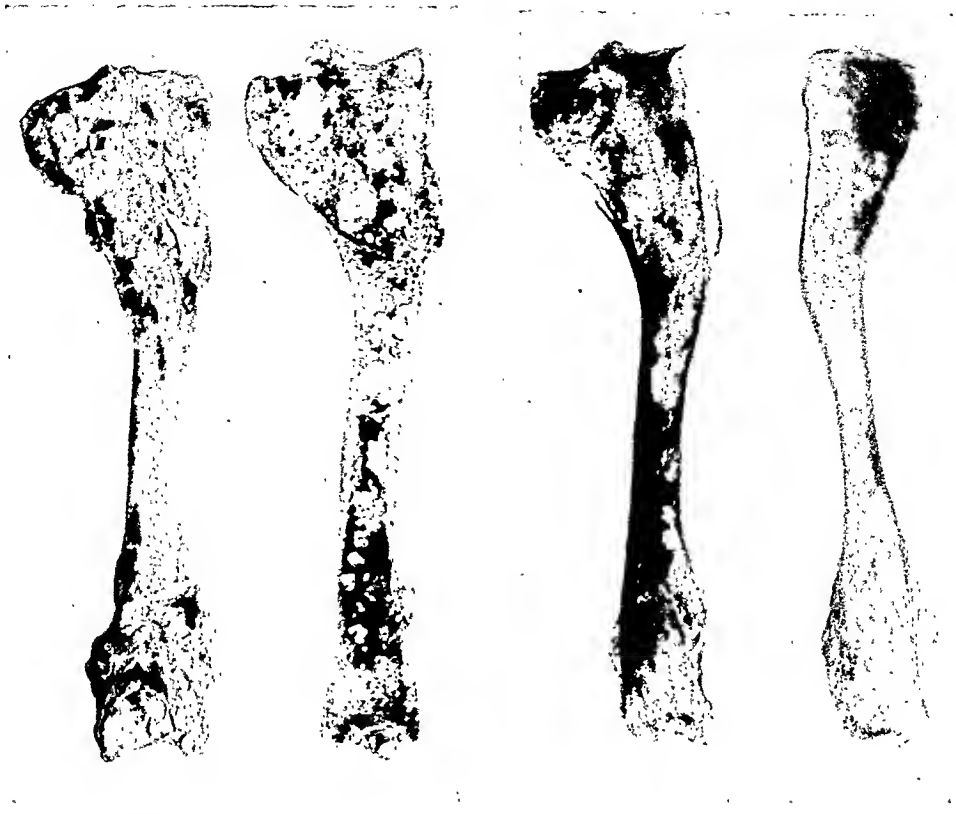


FIG. 29. Case 20. Right tibia showing deformities and chondromata

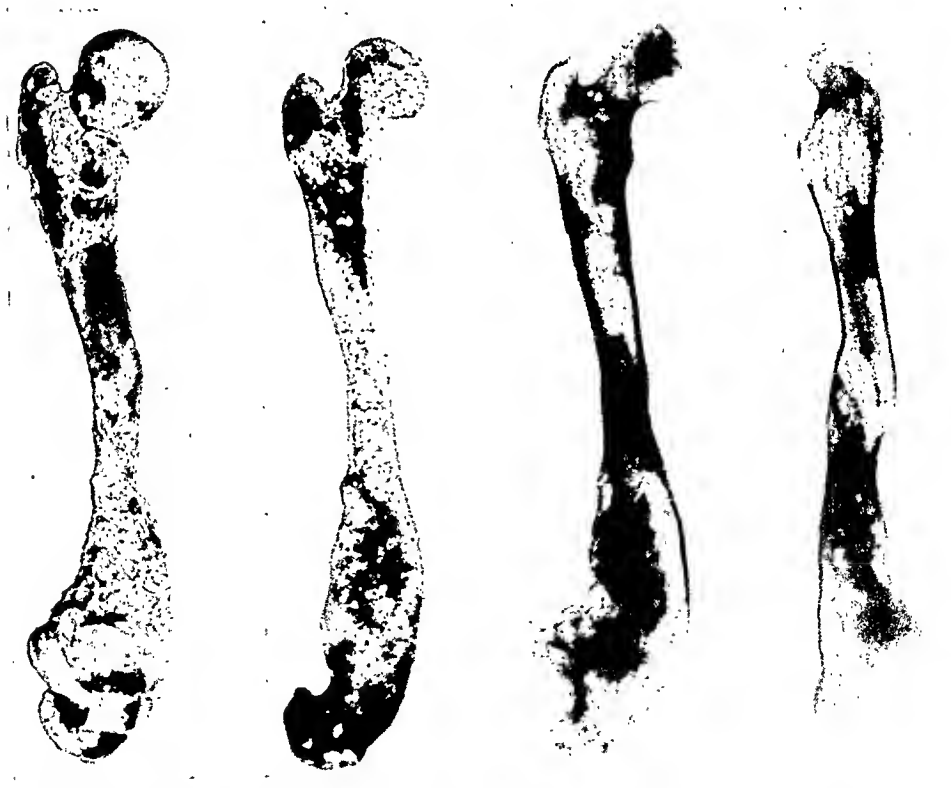
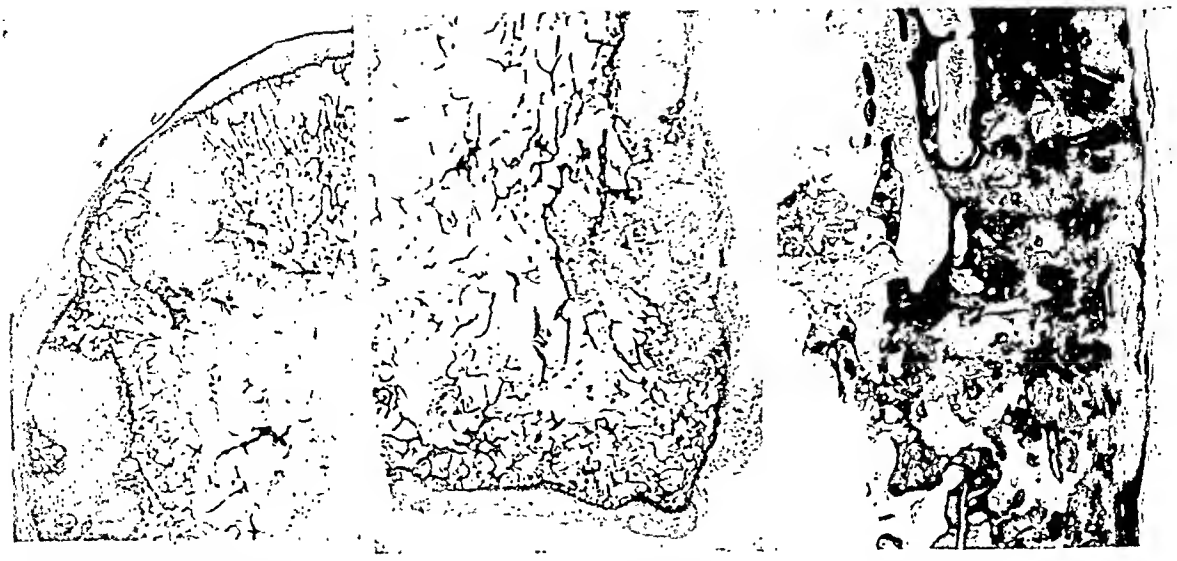
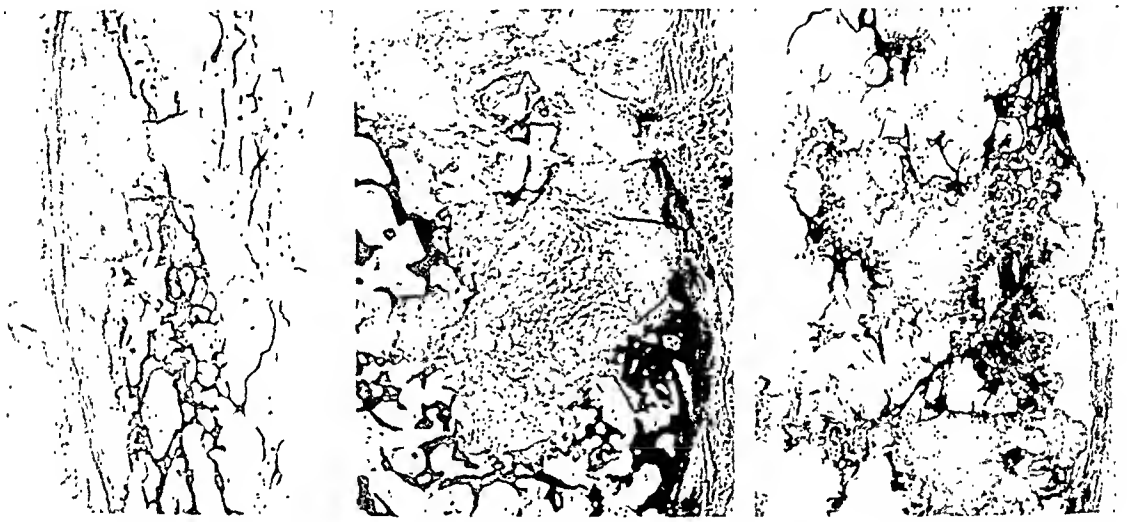


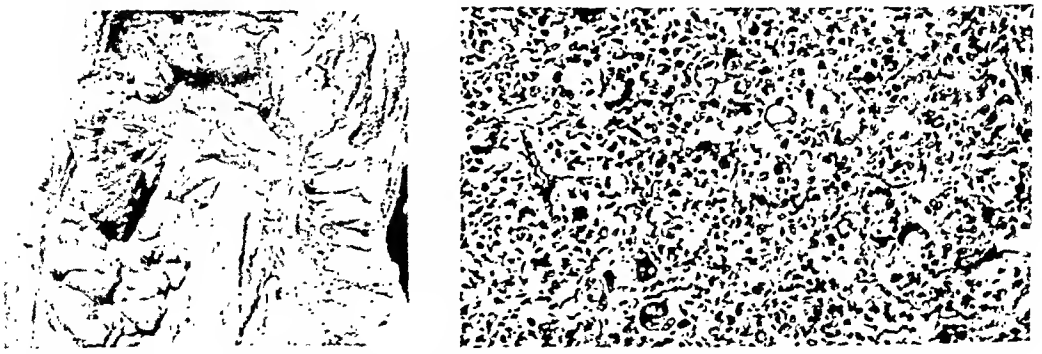
FIG. 30. Case 20. Right femur showing deformities, chondromatous areas, and irregularities of the trabecular structure. The lateral skiagraph shows the deformity of the shaft resulting from an old fracture



FIGS. 31–3. 31. Case 20. A section of the lower condyle of the femur showing normal articular cartilage and much normal trabecular bone, but just lateral to the articular surface there is a large mass of cartilage and in the shaft there is a zone of cartilage persisting in the position of the corticalis (haematoxylin and van Gieson, × 2·5). 32. A section of the lower end of the tibia including the articular cartilage, which is normal. In the shaft there are large zones of cartilage persisting in the corticalis, but the bony trabeculae of the medulla are comparatively normal (haematoxylin and van Gieson, × 3). 33. Case 20. A section of the femoral shaft showing the persistence of areas of cartilage in the comparatively normal compact bone of the corticalis; there is also cartilage in some of the trabeculae (haematoxylin and van Gieson, × 8)



FIGS. 34–6. 34. Case 20. A section of the lower end of the tibial shaft showing the persistence of a large zone of cartilage in the corticalis which is covered on the medullary surface with lamellar bone from which arise fairly normal trabeculae (haematoxylin and van Gieson, × 3). 35. Higher magnification of a portion of Fig. 32 showing the irregular character of the cartilage cells and the sharp demarcation between the lamellar bone and the cartilage (haematoxylin and van Gieson, × 12). 36. Case 20. A section of the lower third of the lateral surface of the femoral shaft showing normal cortical bone at one point merging into an area where there has been persistence of cartilage and no cortical bone whatever, although the fibrous periosteum is considerably thickened. In the medullary cavity the persistence of cartilage in the trabeculae has caused them to be broadened and distorted (haematoxylin and van Gieson, × 3)



FIGS. 37–8. 37. Case 20. The meninges showing angeiomata and phlebectasia. 38. Case 20. A cellular area in the cerebral glioma showing multinuclear cells and nuclear inclusions

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LOCALIZED PRETIBIAL MYXOEDEMA IN ASSOCIATION WITH TOXIC GOITRE[1]

By W. R. TROTTER and K. C. EDEN

(From the Medical and Surgical Units, University College Hospital)

With Plate 20

The facts that excess of mucin is found in the skin of adults in two apparently opposite conditions, namely hypothyroidism (generalized myxoedema) and toxic goitre (localized pretibial myxoedema), and that apart from these two diseases it practically never occurs, pose a problem sufficiently odd to justify more discussion and investigation than the subject has hitherto received. This relative neglect is no doubt due to the fact that localized pretibial myxoedema is mainly known only to dermatologists, who themselves have little opportunity of studying it against the wider background of thyroid disease. It is a striking fact that whereas the condition is fully described in almost all the larger dermatological text-books, we can find no mention of it in the standard works on thyroid disease, apart from a brief reference by Bram (1936) and a fuller account by Netherton in Crile's (1932) book. Dunhill (1937), in his Lettsomian Lectures, gives a short description based on seven of his own cases. It is with the object of attracting the attention of those interested in thyroid disease to a subject too long neglected that we are presenting in the present paper a summary of the known facts concerning localized myxoedema.

So far as we are aware, the first recognizable description of localized pretibial myxoedema was by Watson-Williams (1895). The account is a brief one, but sufficiently clear to justify the assumption that his was a genuine case. Watson-Williams also referred to a similar case described by Hektoen, but we have been unable to trace the reference. Four years later Morrow (1899) gave a much fuller account of another case. The condition then appears to have been lost sight of till Richter's (1927) paper re-awakened interest in the subject. We have been able to discover records of altogether 73 cases of localized pretibial myxoedema. Apart from those referred to above, the following authors have described cases: Arzt (1934), Bamber (1937), Carol (1932), Dowling (1934 *a*, *b*), Dunhill (1935, 1937, 7 cases), Ebert and Wolf (1934), Edel (1935), Freund (1931 *a*, *b*), Gammel and Binkley (1935), Gardner (1934), Goldner (1930), Gottron (1935), Handley and Downing (1939), Hecht-Eleda (1937, 2 cases), Ingram (1933), Keining (1928, 1930),

[1] Received May 12, 1942.

Königstein (1931), Lord and Morrison (1933), McEwan (1938), McMenemey (1933), Marchionini and Jahn (1938), Minzlaff (1935, 8 cases), Netherton and Mulvey (1935, 6 cases), O'Leary (1930, 8 cases), Pierini (1938), Pillsbury and Stokes (1931, 3 cases), Postma (1935), Richter (1931), Riehl (1937), Robinson (1934), Samek (1928), Sandbacka-Holmström (1936), Schönfeld (1937), Schuermann (1938), Schwartz and Maddren (1941, 2 cases), Urbach (1930), Westphalen (1927), and Zoon (1933). Since the majority of these authors describe single cases, it seems that the condition is regarded as a rarity. It is interesting to note that of the 45 papers referred to above, 34 appeared in dermatological journals. Not all of these papers give as full an account of the cases as could be wished, while a few (notably Minzlaff's) were not accessible to us in an unabbreviated form. Four further cases are briefly described in the appendix to the present paper.

Incidence

No case of localized pretibial myxoedema has been described in a patient without past or present thyrotoxicosis. In the majority of cases the goitre seems to have been of the toxic diffuse type (primary thyrotoxicosis, exophthalmic goitre), as it was in our four cases. However, Hecht-Eleda (1937), Netherton and Mulvey (1935), and Schwartz and Maddren (1941) each record a case in which a toxic nodular goitre (secondary thyrotoxicosis, toxic adenoma) is said to have been present. Our own four cases occurred in a series of 130 cases of toxic diffuse goitre. It therefore seems that the incidence of localized pretibial myxoedema in this type of goitre is of the order of three per cent., but it must be remembered that in this series the legs were examined as a routine; Case 3, and possibly Case 2, would not otherwise have been detected. We are not aware of any other published statement of the incidence in a series of cases of toxic goitre; but Dunhill (personal communication) informs us that the incidence in his much larger series was similar to that in our own. We have found records of the patient's age in 55 cases and sex in 57 cases, and from these Tables I and II have been constructed. The age and sex incidence of the whole series of 130 cases of toxic diffuse goitre is given for comparison.

TABLE I

Age Incidence of 55 Cases of Localized Pretibial Myxoedema, compared with that of 130 Cases of Toxic Diffuse Goitre

Age in years	Localized pretibial myxoedema (incidence per cent.)	Toxic diffuse goitre (incidence per cent.)
Below 20	0	11
20 to 29	16	28
30 to 39	24	25
40 to 49	31	21
50 to 59	16	14
Over 60	13	1

TABLE II

Sex Incidence of 57 Cases of Localized Pretibial Myxoedema, compared with that of 130 Cases of Toxic Diffuse Goitre

	Number of males	Male/female ratio
Localized pretibial myxoedema	20	1/1·8
Toxic diffuse goitre	24	1/4·4

It will be seen from Table I that cases with localized pretibial myxoedema tend to be older than cases of toxic diffuse goitre in general, and from Table II that there is, as Schuermann (1938) pointed out, a higher proportion of males. The great majority of cases seem to have occurred in persons of European stock, but Schwartz and Maddren (1941) have recorded a case in a Chinese, and Pillsbury and Stokes (1931) and Gammel and Binkley (1935) one each in a negro.

Onset in Relation to Thyrotoxicosis

Data concerning the time of onset are available in 69 cases. In 32 localized pretibial myxoedema appeared before treatment of the thyrotoxicosis, in two after X-ray treatment, and in 35 after thyroidectomy. In 11 of the 35 cases, however, the thyrotoxicosis had recurred when the pretibial lesions were first detected, while in some of the remainder it is evident that all signs of thyrotoxicosis had not been abolished by the operation. Among the cases operated upon there is, therefore, a high proportion of residual and recurrent thyrotoxicosis. Nevertheless, in some cases all signs of thyrotoxicosis had disappeared by the time the pretibial lesions developed, while in five cases actual signs of hypothyroidism were present, with lowering of the basal metabolic rate to between −12 and −30 per cent. In interpreting the above data a possible fallacy to be borne in mind is that the early stages of the lesions may easily be overlooked. In Case 4 of the present series, for instance, it is clear from notes made at the time that the lesions were in existence before thyroidectomy, although their nature was not recognized until much later when they had become more pronounced; and this happened in spite of the fact that we were on the alert for cases of this type. Probably, therefore, some of the lesions recorded as first appearing after thyroidectomy had actually been present before operation. Nevertheless, it seems clear that localized pretibial myxoedema may appear at any stage in the course of a case of toxic diffuse goitre, although it is most commonly found during a phase of active thyrotoxicosis. It cannot therefore be the result either of general hypothyroidism or of thyrotoxicosis. It also seems that localized pretibial myxoedema is particularly prone to occur in cases of recurrent or residual thyrotoxicosis. A further small point, which may or may not be significant, is that in three cases (Schuermann, 1938; Marchionini and Jahn, 1938; Case 2 of the present series) exophthalmos and localized pretibial myxoedema developed simultaneously after thyroidectomy.

Pathology

The histological features of localized pretibial myxoedema have frequently been described; Pillsbury and Stokes (1931), for example, give a detailed account. In sections stained with haematoxylin and eosin the most conspicuous features are the splitting apart of the connective tissue fibres of the cutis (Plate 20, Fig. 1), and the absence of all signs of inflammation. In sections stained with thionin-blue the substance separating the fibres is seen to stain pink, a reaction regarded as specific for mucin. The skin sections in our cases were prepared and examined by Dr. Freudenthal, and all showed in an unmistakable form the changes described above. In well-marked cases a glairy fluid (presumably mucin) can be seen exuding from the cut surfaces as the biopsy is being performed.

Clinical Features

Patients with localized pretibial myxoedema seldom complain of any symptoms in the legs. In the gross cases there may be some aching of an indefinite sort, and occasionally pricking or tingling sensations. The appearance of the lesions is quite characteristic, and when once seen can readily be recognized, even in early cases. As a rule the lesions first appear on the antero-lateral aspect of the lower half of the legs. Later, they may extend upwards as far as the knee and also to the back of the legs; occasionally also to the dorsum of the feet. The lesions are usually bilateral from the first, and always become so eventually. In the affected areas the skin is raised in irregular, firm swellings, the uneven contours of which are the most characteristic feature of the condition. This unevenness is often best appreciated by touch. The swellings are in the skin rather than beneath it, for the skin cannot be moved independently. The attachment of hair follicles to deeper structures often produces a characteristic dimpled or 'pigskin' appearance. The skin is commonly a faint pink or sometimes brown colour, but is not otherwise altered in colour. In our cases there did not seem to be any gross difference of temperature, but according to Carol (1932) and Sandbacka-Holmström (1936) skin-thermometer measurements show that the affected skin is 2° to 7° C. cooler than the surrounding normal skin. There are no objective sensory changes, and sweating is said by Dowling (1934*a*) to be normal in the region of the swellings. The growth of numerous coarse hairs from the affected skin is a marked feature of some cases.

Course and Treatment

Our impression is that the lesions tend to disappear spontaneously over a period of a few years, but this statement must be accepted with reserve, for there are few accounts available of cases which have been followed for any length of time, and we have not had our own cases under observation long enough to come to a positive conclusion on this point. Since in one of our cases the condition developed and in two others increased after thyroid-

ectomy, we had come to suppose that the usual effect of thyroidectomy was to cause the condition to progress. This is directly contrary to the conclusions of Schuermann (1938) which are based on a personal study of nine cases, including the eight described by Minzlaff (1935). Schuermann states that the lesions tend to progress during a period of active thyrotoxicosis, to regress if this is controlled by operation, and to advance again if a recurrence occurs. Dunhill (1937) says that the condition disappeared completely in six of his seven cases after thyroidectomy, and improved in the seventh. Thyroid extract has been administered to a number of patients, but seems to have been without any clear effect on the lesions. It was given to Cases 2 and 3 of the present series, but we were unable to satisfy ourselves as to the result. Goldner (1930) tried the effect of local injections of thyroxin, which, he said, made the lesions softer and thinner. One such injection was given to our Case 1 (the method used was to inject a fine suspension of free thyroxin, prepared by neutralization of a solution of the sodium salt immediately before use), but the patient would not consent to a second injection and the result was inconclusive. Carol (1932) recommends the use of radiant heat, but this is not supported by any other author. In one of O'Leary's (1930) cases the affected area was excised. This might be a suitable treatment for cases in which the lesions are well defined. Our conclusion is that localized pretibial myxoedema is probably unaffected by any treatment which has yet been employed, and that it follows a fluctuating course, which may lead to eventual disappearance.

Related Conditions

Other types of localized myxoedema. The distinction between the pretibial type and a miscellaneous group of cases described under the general heading of localized myxoedema has been made clear by Pillsbury and Stokes (1931), Carol (1932), and Schuermann (1938). The two main distinguishing features are firstly, that the pretibial type is constantly associated with past or present thyrotoxicosis, an association which, so far as we are aware, has not been recorded in the other group; secondly, that whereas in the pretibial type the lesions are strictly confined to the legs, in the other group they may occur in any part of the body and are only infrequently found in the legs. Furthermore, the lesions in this miscellaneous group are of varied types, macular, papular, and lichenoid, in contradistinction to the constant plaque-like lesions of the pretibial type. The first example of the non-pretibial group now under consideration was described by Dösseker (1916); the small number subsequently recorded is decidedly less than that of the pretibial type. A full account of these cases is to be found in Schuermann's (1938) review.

From the point of view of the present paper the non-pretibial cases may be divided into two groups, according to whether hypothyroidism was present or not. Those with hypothyroidism form the larger group; the cases described by Hoffmann (1923), Bogroff and Krupnikoff (1924), Gougerot, Carteaud, and Eliascheff (1935), and Baranowa (1927) are examples. In these cases

there was a good local and general response to the administration of thyroid extract. It seems reasonable to regard them, as Schuermann (1938) did, as examples of hypothyroidism in which the mucin in the skin has happened to become aggregated in local deposits instead of being uniformly distributed.

Of the second group, in which thyroid function is apparently normal, there are few recorded examples, and Schuermann (1938) regards the condition as very rare. A good description of a case of this sort is given by Per and Rossiansky (1928); here there were no signs of hypothyroidism, the basal metabolic rate was −3 per cent., and a section of the thyroid was substantially normal. We have had the opportunity to study a similar case, which was shown by Dr. Freudenthal at a meeting of the Section of Dermatology of the Royal Society of Medicine (Freudenthal and Brünauer, 1942). In this case there were widespread mucin-containing papules; there were no signs of hypothyroidism, and the basal metabolic rate was +3 per cent. A solitary degeneration cyst of the thyroid was present, and was removed on account of pressure symptoms. At operation the rest of the thyroid was found to be normal in size, and its histological structure was also normal. It therefore seems that it is possible for mucin to be deposited in the skin in the absence of both hypothyroidism and past or present thyrotoxicosis, but it is a rare event.

Hypothyroidism. Ever since Ord (1878) first bestowed the name myxoedema there has been a tendency to assume that the deposition of mucin in the skin is a constant and characteristic feature of hypothyroidism, but it seems in retrospect that Ord was unduly influenced by the single case in his series which came to post-mortem. A piece of skin from the foot of the patient was shown to contain about 50 times as much mucin as that of a control. Ord's case must have been an exceptional one, for when the Myxoedema Committee of the Clinical Society of London (1888) came to examine the results of further analyses, it was found that the average mucin content of the skin of 10 cases of myxoedema was no greater than that of the control cases. On the other hand, in thyroidectomized animals an increased mucin content could almost always be demonstrated. Since that time the question of how frequently an excess of mucin occurs in the skin in hypothyroidism has never been decisively settled. The available evidence is reviewed by Carol (1932) who concludes that the balance of evidence goes to show that while some cases of hypothyroidism have an excess of mucin in the skin, this is far from being a constant feature. Our own scanty experience goes to confirm this, for of four cases of hypothyroidism three showed no histological evidence of mucin (by thionin-blue stain) in skin removed during life from the pretibial region, while the fourth case showed a small quantity. No mucin was found in the pretibial skin of an untreated cretin.

Discussion

From the data presented in the present paper three problems emerge for discussion: the nature of the substance described by the name of mucin, the

factors determining the place of its deposition, and the cause of its being deposited at all.

The nature of mucin. In studies on localized pretibial myxoedema the mucin has been identified solely by histological means, that is, by its reaction to certain stains. The interpretation of these staining reactions is purely empirical and they provide no information in terms of chemistry. So far as we are aware the only chemical investigation undertaken on a case of localized pretibial myxoedema is that of Carol (1932). From a piece of affected skin obtained during life he was able to extract a 'mucin-like' substance, which after hydrolysis with weak acid reduced Fehling's solution. It is obvious that more such investigations are required. Recent developments in biochemistry suggest another approach to the problem, by the use of the enzyme hyaluronidase. Hyaluronic acid (the substance which is hydrolysed by this enzyme) is an important constituent of many mucins; it has been identified in small quantities in normal skin (Chain and Duthie, 1940) and the apparent identity of hyaluronidase and the so-called 'spreading factor' suggests that it is the substance which prevents the diffusion of solutions injected into the skin. It seems likely that hyaluronic acid may also be a constituent of the substance causing the swelling in localized pretibial myxoedema. If it could be shown that the injection of hyaluronidase caused these swellings to disappear important information as to their chemical nature would have been obtained, as well as an effective method of treatment.

The site of deposition of mucin. The constancy with which the lesions appear in the legs implies that, whatever may be the ultimate cause of the deposition of mucin, there must also be an important local factor. Richter (1927), Arzt (1934), and Pillsbury and Stokes (1931) considered that this local factor was the circulatory stasis of cardiac failure. In some of the recorded cases the development of the lesions was apparently preceded by oedema. This was not so in any of our patients nor in many of the recorded cases. The occurrence of congestive cardiac failure, without the subsequent development of localized pretibial myxoedema, is common in toxic goitre and we find it hard to believe that stasis is an important factor. Next to the hands, the shins are perhaps more exposed to repeated trauma than any other area of the body. The idea that this might be the factor determining the site of localized pretibial myxoedema is supported by the fourth case of the present series, for the patient, a gardener, gave a history of repeated minor injuries to the shins, and this was confirmed by the presence of numerous scars in the affected areas. None of our other patients gave a similar history and no evidence in favour of this suggestion is recorded elsewhere. There seems therefore to be no satisfactory explanation of why mucin should be selectively deposited in the pretibial area.

The cause of the deposition of mucin. Most authors who discuss the subject seem to regard the lesions of localized pretibial myxoedema as a manifestation of hypothyroidism. Thus Richter (1931), Carol (1932), Urbach (1930), and Marchionini and Jahn (1938) postulate a state of 'local hypothyroidism'.

Arzt (1934) supposes the lesions to be the relics of a previous hypothyroidism which has been overtaken by the onset of thyrotoxicosis. Keining (1928) and Pillsbury and Stokes (1931) believe that the lesions represent a state of hypothyroidism underlying a dysthyroidism, which is the cause of the toxic symptoms. There is in fact no good reason for supposing that the lesions of localized pretibial myxoedema are in any sense the result of hypothyroidism. The presence of mucin in the skin is not a conspicuous feature of hypothyroidism, and the only constant skin change found in that condition, namely lack of sweating, is not, according to Dowling (1934*a*), found in localized pretibial myxoedema. It seems unlikely that the condition would ever have been attributed to hypothyroidism if it were not for the verbal accident that the term myxoedema has a double meaning, being used on the one hand to denote infiltration of the skin with mucin and on the other to denote the syndrome resulting from lack of thyroid hormone. It is easy to see that this ambiguity may lead to the assumption that the presence of mucin in the skin is invariably the result of hypothyroidism, even when, as in the present instance, there is no other reason for supposing this to be the case.

If the problem is approached without these verbal preconceptions, it can be stated in very simple terms. Mucin is found in the skin in a proportion of cases of hypothyroidism and in a proportion of cases of toxic goitre; apart from these two conditions it is virtually unknown. These are two related diseases, and it would indeed be difficult to believe that the occurrence of mucin in both was no more than a coincidence. It is therefore pertinent to inquire whether these two diseases have any single factor in common. No such factor is at present known, but it is possibly worth recalling that there is a certain amount of circumstantial evidence, summarized by Cope (1938), to support the hypothesis that overactivity of the anterior pituitary gland is the immediate cause of thyrotoxicosis, and that there is also some evidence (Marine, Rosen, and Spark, 1934; Hertz and Oastler, 1936) that destruction of the thyroid by operation or disease is followed by compensatory overactivity of the pituitary. It is therefore possible that pituitary overactivity is common to both toxic goitre and hypothyroidism; and consequently that it may be the cause of the deposition of mucin in these two conditions. Such a theory is wholly unsupported by any direct evidence, but some of the facts presented in the present paper could be explained in this way. For example, localized pretibial myxoedema is constantly associated with the disease toxic goitre, and yet cannot be the direct product of thyroid toxaemia. The high incidence of recurrent thyrotoxicosis suggests that the skin lesions are particularly liable to occur in patients in whom the stimulus to thyroid overaction is unusually powerful or persistent. The occasional simultaneous development of exophthalmos and localized pretibial myxoedema could be explained by such a hypothesis. Although unsupported at present by any weight of evidence this theory will have served its purpose if it has shown how elucidation of the causation of localized pretibial myxoedema might also illuminate more general problems of thyroid pathology.

Our object in writing the present paper is to arouse interest in a condition which might prove, on further investigation, to be of more significance than is now appreciated.

Summary

1. Excess of mucin is found in the skin in hypothyroidism (generalized myxoedema) and in certain cases of toxic goitre, in which it appears in the form of deposits in the legs (localized pretibial myxoedema).

2. Reference is made to 73 previously recorded cases of localized pretibial myxoedema and four fresh cases are described.

3. The incidence, clinical course, and pathological features of the condition are briefly reviewed.

4. Generally, though not invariably, the condition develops at a time when the patient is actively thyrotoxic, and is unaffected by the administration of thyroid extract or by thyroidectomy. It does not therefore seem to be the direct result of either hypothyroidism or thyrotoxicosis.

5. The local and general factors governing the deposition of mucin in the skin are discussed.

We wish to thank Dr. Freudenthal for the preparation and interpretation of the skin sections, and for his general advice and criticism.

APPENDIX

Case Reports

Case 1. A woman, aged 50 years, was first seen on 6.5.38. There had been a history of trembling and breathlessness for one year. She was a typical example of toxic diffuse goitre of moderate severity, although there were no eye signs. The pulse-rate was 90 to 126, and basal metabolic rates were +42 and +44 per cent. There was no congestive cardiac failure or enlargement of the heart, and the legs were not then abnormal.

Operation was advised, but the patient did not then consent. Seven months later she changed her mind, as the symptoms had become worse. Basal metabolic rates were at this time +72 and +66 per cent. The clinical condition was much the same except that swelling of the legs had developed, and extended from the knees to the ankles in both legs (Plate 20, Fig. 2). It was most marked on the front, but was also present on the back of the legs. There was a general thickening of the skin in the affected areas, with irregular swellings projecting here and there above the general level. In the region of these swellings the skin was a faint pink and had a 'pigskin' appearance from the attachment of hair-follicles to deeper structures. Subtotal thyroidectomy was performed on 17.1.39. Sections of the thyroid showed a mild degree of epithelial hyperplasia. After operation the patient was seen on several occasions, and re-admitted for investigation on 11.6.39. There were then no signs of thyrotoxicosis or hypothyroidism. The resting pulse-rate was 84, and basal metabolic rates +18 and +16 per cent. The swelling of the legs had increased, but had not altered in character; it was accompanied by burning sensations and itching. A biopsy showed the typical changes of localized myxoedema. Both the general and local condition remained unchanged until 27.2.40, when it was found that the right lobe of

the thyroid had again become palpable, and that the resting pulse-rate had risen to 100.

Case 2. A woman, aged 40 years, was first seen on 14.10.38 with a history of nervousness and palpitations for the previous nine months. She was a typical example of toxic diffuse goitre of moderate severity, with well-marked lid-retraction. The pulse-rate was 108 to 120, and basal metabolic rates +54, +48, and +48 per cent. There was no congestive cardiac failure and the legs were not abnormal. Subtotal thyroidectomy was performed. Sections showed a moderate degree of epithelial hyperplasia. The basal metabolic rate on discharge was −17 per cent. (7.12.38). While under observation during the next six months there were no signs of thyrotoxicosis and the only hint of hypothyroidism was a slight puffiness of the face. On 17.7.39 she complained of lumps on the legs, which were painless but disfiguring. At this time the legs showed several ill-defined nodules scattered over the front of both shins, each 1 to 2 cm. in diameter. There was the same pinkness and 'pigskin' appearance over these nodules which had been noted in Case 1. A biopsy showed the typical changes of localized myxoedema in skin from the pretibial area, but no mucin in skin from over the sternum. Basal metabolic rates at this time were −10 and −2 per cent.; the plasma-cholesterol was 270 mg. per 100 c.c.

From 31.10.39 to 13.2.40 thyroid extract (B.P.) was administered in a dose of 1 gr. daily, but there was no appreciable change in the local or general condition during this period. No further treatment was given and no further change occurred in the legs until 22.11.40, when it was noted that the lesions were diminishing in size. This diminution continued, and on 22.1.42 the legs were not recognizably abnormal.

Case 3. A woman, aged 56 years, was first seen on 18.3.41. There was a history of ill-health and loss of weight for seven years. She was a typical example of toxic diffuse goitre as it is seen in elderly subjects. Auricular fibrillation was present with a moderate degree of enlargement of the heart, and 2 in. of venous congestion in the neck, but no peripheral oedema. There was bilateral lid retraction. Basal metabolic rates were +48, +44, and +38 per cent.

The skin of both pretibial regions was diffusely thickened. The thickened area was slightly irregular in contour, but there were no prominent nodules. The affected skin was a faint pink colour and the characteristic 'pigskin' appearance was just recognizable. The skin changes in this case were too slight to be identifiable in a photograph, but just sufficient for the clinical diagnosis to be made correctly.

A biopsy of the affected skin showed the typical changes of localized myxoedema. A two-stage total thyroidectomy was performed. Sections of the thyroid showed the changes of lymphadenoid goitre with isolated areas of well-marked epithelial hyperplasia. This case has been reported elsewhere as an example of lymphadenoid goitre with the clinical picture of thyrotoxicosis (Eden and Trotter, 1941). Lid-retraction rapidly disappeared after operation, and regular rhythm was restored with quinidine. The basal metabolic rate on discharge was −6 per cent.

Four months after operation, signs of hypothyroidism were apparent, and the pretibial myxoedema had increased slightly. She was then given thyroid extract (B.P.) 1 gr. daily. This dose has been continued up to the present (Feb., 1942) and seems sufficient to control the hypothyroidism. The skin lesions have decreased in size.

Case 4. A man, aged 55 years, a gardener, was first seen on 11.3.41. There was a history of loss of weight and palpitations for the previous three months. He was a typical example of toxic diffuse goitre with bilateral lid-retraction; there was no congestive cardiac failure and no enlargement of the heart. At this time there was no swelling of the legs, but a number of old scars were present which the patient said were the result of knocks and kicks received during the course of his work as a gardener. A note made at the time states that some of the scars were 'hypertrophic', but we did not think the condition sufficiently like localized myxoedema to justify a biopsy. Basal metabolic rates were +50, +45, and +30 per cent. Subtotal thyroidectomy was performed on 10.4.41. Sections of the thyroid showed a mild degree of epithelial hyperplasia. He was seen on several occasions after thyroidectomy. The general result of the operation was satisfactory, lid-retraction diminished, and there was a substantial gain in weight. No change was noticed in the condition of the legs until 26.2.42. He then stated that he had 'sores' on the legs, which had broken down from time to time. On examination, an indurated area about 5 by 3 in. in size was found on the front of the right leg, situated midway between the knee and the ankle. On the left leg there was a prominent boss in the same situation, about 2 by 3 in. in size, and of the consistency of bone (Plate 20, Fig. 3). Over both these raised areas the skin appeared thickened, irregular in contour, and of a faint pink colour, but the picture was complicated by the presence of old scars in the affected area. The boss on the left leg was so hard as to suggest a syphilitic periostitis, but an X-ray of the leg showed no bony abnormality. A biopsy of the affected skin showed the typical changes of localized myxoedema.

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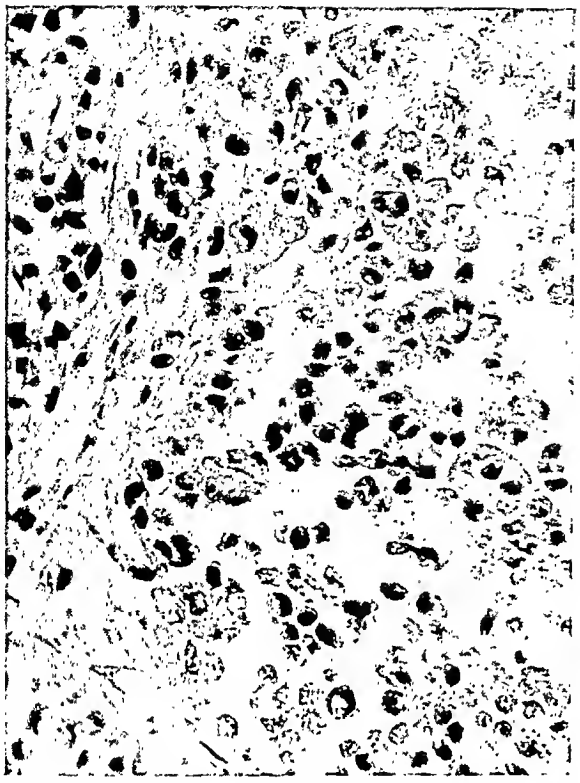

FIG. 1. Low power view of a section of skin from a case of localized pretibial myxoedema (haematoxylin and eosin)

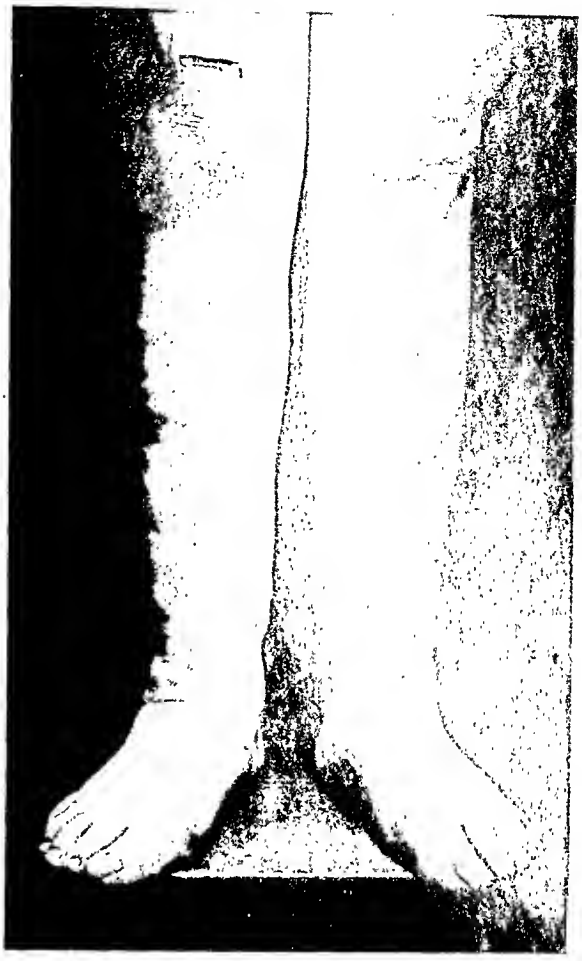

FIG. 2. General appearance of the legs in Case 1

FIG. 3. General appearance of the legs in Case 4

PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1942

THIRTY-SIXTH ANNUAL GENERAL MEETING

THE THIRTY-SIXTH ANNUAL GENERAL MEETING was held at Cambridge in the Department of Physiology on Saturday, 11 April 1942. The attendance book was signed by 83 members. The proceedings began at 10 a.m.

The President, Sir E. Farquhar Buzzard, was in the Chair.

The Minutes of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

The Treasurer presented the Annual Accounts which showed a balance of £995, from which the sum due for the *Quarterly Journal of Medicine* for the last twelve months must be deducted. It was agreed to invest £400 in War Defence Bonds.

Revision of Rule 2. On the proposal of the Honorary Secretary it was agreed that the second paragraph of Rule 2 should be amended to read as follows:

'Extra-Ordinary Members.—Ordinary Members of not less than fifteen years' standing may be elected Extra-Ordinary Members on nomination by the Executive Committee. Such members shall have the rights and privileges of Ordinary Members, but shall not be subject to Rule 20. The number of such members elected annually shall not exceed eight.'

Place of Meeting in 1943. The possibility of a one-day meeting in London was suggested.

Election of Officers

President. Professor J. A. Ryle was elected President, and on taking the Chair expressed the thanks of the Association to the retiring President for his services to medicine both within and outside the Association.

Election of Officers, Executive Committee, Extra-Ordinary Members, and Ordinary Members then followed.

Executive Committee

President. Professor J. A. Ryle.

Treasurer. Professor L. J. Witts.

Secretary. Dr. C. E. Newman.

Members for England:

Dr. A. E. Barnes.
Dr. T. Izod Bennett.
Dr. L. B. Cole.
Dr. J. L. Livingstone.
Dr. J. Parkinson.
Professor L. G. Parsons.

Members for Scotland:

Professor R. S. Aitken.
Professor G. B. Fleming.
Professor D. Murray Lyon.

Members for Ireland:

Dr. F. M. B. Allen.
Dr. G. C. Dockeray.
Dr. J. A. Smyth.

Honorary Members

Sir E. Farquhar Buzzard (President, 1941–2).
Major-General H. Letheby Tidy (Treasurer, 1933–42).

Extra-Ordinary Members

Dr. R. A. Chisholm.
Dr. George Graham.
Dr. Gordon Holmes.
Dr. C. E. Lakin.
Dr. J. C. Rankin.

Ordinary Members

Samuel Harold Cookson, M.D., Physician, Cornelia and East Dorset Hospital, Poole.
John Baxter Gaylor, F.R.F.P.S., Assistant to Regius Professor of Medicine, Glasgow University.
James Gilbert Murdoch Hamilton, F.R.C.P.E., Assistant Physician, Royal Infirmary, Edinburgh.
Swithin Pinder Meadows, M.D., Assistant Physician, Westminster Hospital.
Herbert Victor Morlock, M.D., Physician, London Chest Hospital.
Frederick Murgatroyd, M.R.C.P., Assistant Physician, Hospital for Tropical Diseases.
Wilfred George Oakley, M.D., Assistant Physician, Diabetic Department, King's College Hospital.
Max Leonard Rosenheim, M.D., First Assistant, Medical Unit, University College Hospital.
Edward Peter Sharpey-Schafer, M.R.C.P., First Assistant, Department of Medicine, British Postgraduate Medical School.
Claude Howard Whittle, M.D., Physician, Addenbrooke's Hospital, Cambridge.

SCIENTIFIC BUSINESS

Saturday Morning

1. Dr. S. Alstead described *The Adsorbent Action of Charcoal and its Clinical Application.* In many hospitals the nuisance of offensive smells associated with foul discharges constitutes a major problem. Although the local application of charcoal is effective in cleansing an ulcer, it usually fails as a deodorant because the discharge leaks through the dressing. Activated charcoal of suitable mesh can be dispersed in hospital wadding and used as a blanket. Clinical trials and experimental observations show that charcoal employed in this way is very effective as a deodorant.

Professor McNee referred to the use of gauze dressings impregnated with charcoal and Dr. K. D. Wilkinson mentioned war researches on materials of this type. In reply to questions from Professors Ryle and Himsworth, and Dr. Cooke, Dr. Alstead said that the blankets could be autoclaved but not washed; the specification of the charcoal was 'guaranteed activated charcoal'; and inactivation was not a problem, as the charcoal lasted longer than the blanket.

2. Dr. Ferguson Anderson (introduced) and Professor Noah Morris made *Some Observations on the Pharmacology of Gastric Motility in Man.* The gastric movements in the fasting subject were recorded by a modification of Carlson's method. The water reversal phenomenon, consisting of complete inhibition of gastric movements after the ingestion of water, is not observed in patients with peptic ulcer, in whom the swallowing of water produces an increased gastric motility. Atropine in small doses increases gastric contraction and has a sedative effect only when the intravenous dose exceeds 0·4 mg. and the subcutaneous 1·0 mg. Two small doses at half-hourly intervals have a total effect which is much more powerful than if given together in one injection. It is suggested that the first dose sensitizes the neuromuscular apparatus. Syntropan and Trasentin have sedative effects on the stomach, but do not significantly influence the pulse rate. Strychnine hydrochloride given hypodermically in doses of gr. 1/20 increases gastric motility, but does not apparently influence appetite as judged by subjective sensations or by the weight chart.

In reply to Dr. Geoffrey Bourne and Major-General Tidy, Professor Morris stated that the action of a second dose of atropine could be explained only by sensitization and not by accumulation. He had not studied the effect of water on chronic gastric dyspepsia.

3. Dr. L. B. Cole described a case of *Trichobezoar in a Girl of Six Years*. Her habit of eating hair developed at the age of three years, lasted for a year, and recurred later for a few months. Her mentality appeared to be normal. Diagnostic points stressed were the shape of the tumour like a firm cast of the normal stomach, the normal sedimentation rate, and the radiological appearance. Preliminary treatment with iron cured her anaemia before operation. Two tumours were successfully removed which when fitted together formed a complete cast of the stomach.

Sir Philip Manson-Bahr described the successful removal of a hair-ball from the stomach of a peregrine falcon.

4. Sir Edmund Spriggs spoke on *Polyps and Polypoids of the Stomach*. He demonstrated radiographs, drawings from gastroscopy, and drawings and photographs of pathological specimens, from 70 cases of polyps of the stomach of varying nature. Eleven cases were observed at Ruthin Castle in 4,424 X-ray examinations. The rest were communicated by interested colleagues and the curators of museums. All the cases, except three, were hitherto unpublished. The term polyadenoma or the more general term polyposis was applied to 18 cases with such a number of polyps as were not easily counted. He also reviewed 21 cases with gross hypertrophic gastritic swellings. Clinical features, pathology, treatment, and prognosis were briefly discussed.

Dr. Hobson described a case of gastric polyposis which had been quoted as evidence of the success of a cancer cure, but was again under treatment for haemorrhage. Professor Ryle mentioned the symptom of sudden pyloric stenosis. Professor Christie described the association of gastric polyposis with idiopathic low-protein oedema, Professor Himsworth that with aplastic anaemia, and Dr. Ungley that with pernicious anaemia. Sir Edmund Spriggs had had no cases of pernicious anaemia in his series.

5. Dr. W. Jacobson (introduced) and Dr. L. B. Cole described the *Effect of Spleen Extract in Erythraemia*. Examination of the bone marrow obtained by sternal puncture from three cases of erythraemia showed a considerable increase in erythroblastic mitoses. Small fragments of this marrow were grown *in vitro* with spleen or liver extracts from a guinea-pig. When the marrow was grown with spleen extract no erythroblastic mitoses occurred after 24 hours and large numbers of red cells were destroyed during the second and third day, but marrow growth with liver extract continued to show erythroblastic mitoses. The three cases were treated with weekly doses of 150 to 250 c.c. of a saline extract of minced pig's spleen given by mouth, and the red-cell counts dropped from 9·35 to 6·35 millions per c.mm. in six weeks, from 9·25 to 6·2 millions in 12 weeks, and from 10·05 to 6·65 millions in seven weeks. Before treatment the red-cell count had consistently risen except when regular treatment with phenylhydrazine or venesection had been given. The regulating influence of the spleen on the activity of the bone marrow was further illustrated by the observation that whereas normal rabbits do not show a reticulocyte response after the injection of haemopoietic substances, splenectomized rabbits give a repeated reticulocyte response.

6. Dr. H. W. Fullerton discussed *Pernicious Anaemia of Pregnancy and the Puerperium*. Injection of crude and refined liver extracts produced a reticulocytosis, but little or no rise in the blood count in three cases of severe macrocytic anaemia of pregnancy and the puerperium. Rapid blood regeneration followed treatment with whole liver and liver extracts parenterally. It was suggested that there was deficiency not only of the anti-anaemia principle, but also of hitherto undefined factors present in whole liver, but not in extracts for parenteral administration.

7. Miss Sheila Callender also discussed *Pernicious Anaemia of Pregnancy*. The blood findings and some of the characteristic features of 23 cases of pernicious anaemia of pregnancy were reviewed. Though a macrocytic blood picture may occur, the anaemia is frequently normocytic, with a normal or even low colour index. Variability in the blood picture may make sternal puncture the only certain method of diagnosis, a characteristic megaloblastic marrow being found. Ten of the cases were associated with sepsis. The results of treatment with liver extract, plus transfusion in some cases, were good, but there tended to be some delay in response where sepsis was present. One patient required in addition oral liver therapy.

Professor Davidson described a series of cases of pernicious anaemia of pregnancy, emphasizing the value of persistent treatment until the refractory phase had been overcome.

Luncheon

Luncheon, which again took the place of the Annual Dinner of peace time, was held in Caius College. There were present 91 members and guests. The President proposed the toast of the Association, speaking of our brave defenders, who had made the meeting possible, and of the historic medical associations of the College.

2.30 p.m. *Afternoon Session*

1. Dr. Hugh Barber showed *Some Electrocardiograms of Trauma.* A series of 33 hospital accident-cases was examined, irrespective of symptoms, within 48 hours of injury. Crushing injuries of the thorax and severe blows over the chest were selected. The electrocardiograms showed one example of partial heart block, one of sinus bradycardia, one of slurring of the R waves, and five of temporary changes in the T waves. These changes were analogous with results published by those who have experimented with heart trauma in animals, and their claim for the necessity of an early examination was confirmed.

Dr. J. M. H. Campbell agreed that traumatic lesions of the heart were more common than was formerly thought.

2. Professor Crighton Bramwell described *Relative Mitral Stenosis.* He discussed the clinical findings in 157 recruits in whom there was a systolic murmur with duplication of the second heart sound at the apex. In a group of 828 recruits referred to him by Medical Boards these signs occurred in 32 per cent. of those under 25 years of age and in only 10 per cent. over that age. Seventy per cent. were regarded as fit for Grade I. Professor Bramwell emphasized the fact that the production of an obstructive murmur depended on the degree of obstruction relative to the rate of blood-flow through the obstructed orifice, and suggested that duplication of the second heart sound signified that the mitral orifice was relatively too small for the blood-flow when the rate of venous return to the heart was increased. He believed that the same was true of the roughening and accentuation of the first heart sound in many cases of thyrotoxicosis and in other conditions in which the heart was overactive. He considered that neither of these signs indicated an organic mitral lesion.

Dr. William Evans pointed out that the presence of a third heart sound in healthy people was correlated with retention of the contour of the child's heart. Dr. Parkinson agreed that the third heart sound was frequently heard if listened for, but thought that a duplicated first sound was more often mistaken for mitral stenosis. Major-General Tidy asked whether these results should not be made more widely known, but Dr. Bourne deprecated the use of the term 'relative mitral stenosis'.

3. Dr. Geoffrey Bourne described *Six Cases of Infected Ductus Arteriosus treated by Ligation.* The first case (Dr. Keele's) was the first recorded to be so treated. The infection here was *H. para-influenzae.* The organism isolated from the other five cases was streptococcus viridans. Two cases are alive and well, 27 and 17 months after ligature. Three of the others are alive, two are well, and one is convalescent. There was one death six weeks after operation. There was no surgical fatality. Ligature alone was curative in one case. In another where chemotherapy had been quite ineffective ligature was curative.

Mr. O. S. Tubbs discussed the surgical problems encountered in the six patients described by Dr. Bourne. Prior to the operation on the first case in December 1939, it was not known how ligation would affect the infection or whether the infection would complicate the operation. He then outlined and illustrated the technique used, emphasizing the necessity for gentleness in isolating the ductus which might be friable as a result of the infection. The rationale of the operation remained unexplained, but the results had justified the experiment.

Sir Joseph Barcroft described the closure of the ductus arteriosus in the foetus and inquired about the shape and size of the ductus before ligation in man. Dr. Sharpey-Schafer pointed out that though the shunt was associated with a rise in blood-volume, parenteral fluid was well tolerated and should not be denied at operation.

4. Brigadier A. W. Stott and Dr. P. Kerley (introduced) described the *Pulmonary Changes in Erythema Nodosum.* Pulmonary changes are common in erythema nodosum, but they seldom give rise to symptoms or physical signs. Enlargement, sometimes massive, of the bronchial glands has long been known and many have accepted it as

evidence of a tuberculous aetiology. Less familiar is infiltration of the lung and of this there are three varieties: (*a*) a nodular form resembling miliary tuberculosis, (*b*) a coarse striation radiating from the hila, and (*c*) a segmental area of consolidation which may be due to collapse. These pulmonary changes appear to be identical with those found in the sarcoidosis of Boeck, and several cases of this disease have been described in which the onset was with an illness and rash resembling erythema nodosum.

DR. WHITTLE described another case of erythema nodosum associated with sarcoidosis. DR. MARTIN described a similar rash and bony changes in a case presumably meningococcal in origin. DR. R. E. SMITH thought it would be unwise to minimize the importance of tuberculosis in this syndrome.

5. SURGEON-COMMANDER C. C. UNGLEY described *Immersion Feet and Allied Conditions After Exposure to Cold.* In immersion foot long exposure to cold insufficient to freeze tissues, for example, sea at 0° to 8° C., for 20 hours or more, causes damage, direct or indirect, to nerves, vessels, skin, muscle, and even bone. Feet or hands, pale and slightly swollen on rescue, later become hot, red, tender, and more swollen, and also tingle and ache. Lightning pains often begin seven to 10 days later. Findings may include blisters or gangrene, especially if the feet are heated on rescue, motor paresis, wasting, and reaction of degeneration; loss of vibration and joint sense, and of touch, pain, heat and cold in glove and sock distribution, more volar than dorsal; vasomotor and sudomotor disorders, paresis and later hyperactivity. Recovery, except in mild cases, depends on rate of nerve regeneration.

In reply to questions from PROFESSOR HIMSWORTH and DR. BYWATERS, DR. UNGLEY said that he had carried out vasomotor tests such as the goose-flesh test in these cases; he had not observed any general metabolic changes.

6. DR. R. A. MCCANCE and DR. W. F. YOUNG (introduced) discussed the *Function of the Kidney during the First Year of Life.* A study of the secretion of urine in infancy has shown that below the age of one year certain functions of the kidney differ from those of adult life and that the organ as a whole is less efficient. The glomerular filtration rates and the urea and other clearances have been found to be low by adult standards, and the concentration of organic and mineral substances in the urine was low even when the urine volumes were small. Function develops with age, and is at its worst in premature babies. These findings help to explain why premature infants are so susceptible to oedema and why young children tolerate dehydration so badly. For some time after birth a low urine volume is synonymous with renal failure.

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